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=> s detection assay

L1 3562 DETECTION ASSAY

=> s l1 and VEGF-D antibody

L2 0 L1 AND VEGF-D ANTIBODY

=> s l1, and antibody

L3 865 L1 AND ANTIBODY

=> s l3 and VEGF-D

L4 0 L3 AND VEGF-D

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L5 0 L3 AND VEGF

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L6 0 L1 AND ANTI-VEGF

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L7 2622989 ANTIBOD?

=> s l7 and VEGF-D

L8 150 L7 AND VEGF-D

=> s l8 and cancer

L9 60 L8 AND CANCER

=> s l9 and brain

L10 8 L9 AND BRAIN

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L11 5 DUP REMOVE L10 (3 DUPLICATES REMOVED)

=> d l1 1-5 cbib abs

L1 ANSWER 1 OF 3562 MEDLINE on STN

2004570983. PubMed ID: 15488624. Sensitive and reliable detection of grapevine fanleaf virus in a single Xiphinema index nematode vector. Demangeat Gerard; Komar Veronique; Cornuet Pascal; Esmenjaud Daniel; Fuchs Marc. (Laboratoire de Virologie, Institut National de la Recherche Agronomique, Unite Mixte de Recherche INRA-Universite Louis Pasteur 'Vigne et Vins d'Alsace', 28 rue de Herrlisheim, 68021 Colmar, France.. demangea@colmar.inra.fr) . Journal of virological methods, (2004 Dec 1) 122 (1) 79-86. Journal code: 8005839. ISSN: 0166-0934. Pub. country: Netherlands. Language: English.

AB Grapevine fanleaf virus (GFLV) is specifically transmitted from plant to plant by the ectoparasitic nematode Xiphinema index. A sensitive and reliable procedure was developed to readily detect GFLV in a single viruliferous X. index, regardless of the nematode origin, i.e. greenhouse

rearings or vineyard soils. The assay is based on bead milling to disrupt nematodes extracted from soil samples, solid-phase extraction of total nematode RNAs, and amplification of a 555bp fragment of the coat protein (CP) gene by reverse transcription-polymerase chain reaction with two primers designed from conserved sequences. This procedure is sensitive since the CP gene fragment is amplified from an artificial sample consisting of one viruliferous nematode mixed with 3000 aviruliferous individuals. In addition, StyI RFLP analysis of the CP amplicon enables the GFLV isolate carried by a single viruliferous X. index to be characterized. This GFLV **detection assay** opens new avenues for epidemiological studies and for molecular investigations on the mechanism of X. index-mediated GFLV transmission.

L1 ANSWER 2 OF 3562 MEDLINE on STN

2004550027. PubMed ID: 15521846. The new DR-70 immunoassay detects cancer of the gastrointestinal tract: a validation study. Kerber A; Trojan J; Herrlinger K; Zgouras D; Caspary W F; Braden B. (Medical Department II, University Hospital, Frankfurt/Main, Germany.) *Alimentary pharmacology & therapeutics*, (2004 Nov 1) 20 (9) 983-7. Journal code: 8707234. ISSN: 0269-2813. Pub. country: England: United Kingdom. Language: English.

AB Summary Background : Malignant cells characteristically possess high levels of plasminogen activator, which induce local fibrinolysis. The DR-70 immunoassay is a newly developed test, which quantifies fibrin degradation products in serum by a proprietary antibody. Aim : To evaluate the DR-70 immunoassay as a **detection assay** for the presence of gastrointestinal cancers. Methods : We prospectively collected blood sera of 85 patients with histologically proven tumour and 100 healthy blood donors. Ten microlitres of the sera was used for the DR-70 immunoassay. Nineteen patients had a hepatocellular and 10 cholangiocellular carcinoma, 13 cancer of the pancreas, 30 colorectal cancer, 10 stomach cancer and three cancer of the oesophagus. Results : Receiver-operator curve analysis revealed <0.7 mug/mL as the best cut-off value to distinguish between patients with cancer and healthy controls. Using this cut-off value, the DR-70 immunoassay showed a good clinical performance with a sensitivity of 91% and a specificity of 93%. Patients with advanced tumour spread showed significantly higher DR-70 values than those with early-stage tumours ($P < 0.0003$). Conclusion : The DR-70 immunoassay reliably differs between cancer patients and healthy controls. Therefore, it promises to become a useful test for the detection of cancer in clinical practice.

L1 ANSWER 3 OF 3562 MEDLINE on STN

2004549007. PubMed ID: 15519709. Foot-and-mouth disease polyvalent oil vaccines inoculated repeatedly in cattle do not induce detectable antibodies to non-structural proteins when evaluated by various assays. Espinoza Ana M; Maradei Eduardo; Mattion Nora; Cadenazzi Graciela; Maddonni Gabriela; Robiolo Blanca; Torre Jose La; Bellinzoni Rodolfo; Smitsaart Eliana. (Biogenesis S.A. Ruta Panamericana Km 38,2 (B1619 IEA) Garin, Provincia de Buenos Aires, Argentina.) *Vaccine*, (2004 Nov 15) 23 (1) 69-77. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

AB The use of foot-and-mouth disease (FMD) vaccines that do not induce antibodies against non-structural proteins (NSP) is extremely relevant for the demonstration of regions "free of FMDV infection" and control strategies. In this study cattle were primed and boosted with five doses of oil vaccines containing high antigenic payloads on days 0, 90, 130, 160 and 200. The serological response against NSP was measured using four commercially available assays: two 3ABC-ELISAs; one 3B-ELISA (and complementary 3A-ELISA) and an enzyme-immunotransfer blot assay (EITB). Additionally, locally produced NSP antibodies detection reagents and VIAA antibodies were evaluated. A high level of specific immune response against vaccine strains was shown. After four doses of vaccine, non-reactive animals were detected by any of the NSP assays. After the fifth immunization, 2 of 17 animals were reactive in one ELISA kit, but these samples proved negative by confirmatory tests. Antibodies against

NSP were not detected in single dose immunized cattle. The principle of the NSP-ELISA used as a screening test for large sero-surveys in South America is established and this paper emphasizes the importance of using vaccines that have demonstrated no interference with NSP antibodies **detection assays.**

L1 ANSWER 4 OF 3562 MEDLINE on STN

2004528847. PubMed ID: 15481969. Preparation of steroid antibodies and parallel detection of multianabolic steroid abuse with conjugated hapten microarray. Du Hongwu; Lu Yuan; Yang Weiping; Wu Moutian; Wang Jun; Zhao Shan; Pan Mangeng; Cheng Jing. (Department of Biological Sciences and Biotechnology and Institute of Biomedicine, Tsinghua University, Beijing 100084, P.R. China.) Analytical chemistry, (2004 Oct 15) 76 (20) 6166-71. Journal code: 0370536. ISSN: 0003-2700. Pub. country: United States. Language: English.

AB A conjugated hapten microarray based on miniature immunoassay for fast and multiplex detection of anabolic steroids is reported for the first time. This preliminary study investigated the possibility of using a microarray technology as a multisteroid **detection assay**. The microarray system used eight monoclonal antibodies raised against three steroid conjugates, 4-androsten-4-chloro-17beta-ol-3-one, 1,5alpha-androsten-1beta-methyl-17beta-ol-3-one, and 5beta-androsten-1-en-17beta-ol-3-one, which were conjugated to BSA by the active ester method. In addition to 4 commercial conjugated haptens, 18 steroid-BSA conjugates were synthesized and from all these a conjugated hapten microarray was fabricated. The analyzed substances included 42 types of anabolic steroid reference materials and 28 positive urine samples. Of these, 24 anabolic steroids and 12 positive urines were successfully detected.

L1 ANSWER 5 OF 3562 MEDLINE on STN

2004520517. PubMed ID: 15491975. Post-PCR multiplex fluorescent ligation **detection assay** and flow cytometry for rapid detection of gene-specific translocations in leukemia. Chen I-Ming; Chakerian Artemis; Combs David; Garner Kelly; Viswanatha David S. (Department of Pathology, University of New Mexico, Health Science Center, Albuquerque, NM, USA.) American journal of clinical pathology, (2004 Nov) 122 (5) 783-93. Journal code: 0370470. ISSN: 0002-9173. Pub. country: United States. Language: English.

AB We describe a novel method to detect specific polymerase chain reaction (PCR) target amplicons, involving thermostable ligation of fluorescent and biotinylated oligonucleotides, microparticle bead capture of the ligated products, and flow cytometric analysis. This approach, termed fluorescent ligation detection reaction (f-LDR) is more rapid and cost-effective than oligoprobe Southern blot hybridization (SBH). A standard f-LDR protocol was developed to detect the leukemia-associated chimeric transcripts bcr-abl and promyelocytic leukemia-retinoic acid receptor a (PML-RARalpha) in 2 multiplex and multicolor assays. The f-LDR platform was 100% specific and demonstrated comparable or better sensitivity than standard oligoprobe SBH. The usefulness of f-LDR was evaluated in 94 posttherapy samples from 13 patients with acute promyelocytic leukemia with the PML-RARalpha gene fusion. The f-LDR method was highly concordant (93%) with oligoprobe SBH; essentially all discrepancies were noted to be due to the enhanced sensitivity of f-LDR. We conclude that f-LDR is a highly specific and sensitive post-PCR method with wide potential application.

=> s 18 and anti-VEGF

L12 23 L8 AND ANTI-VEGF

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L13 12 DUP REMOVE L12 (11 DUPLICATES REMOVED)

=> d l13 1-12 cbib abs

L13 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2004 ACS on STN

2004:905599 Methods for the use of VEGF-C or **VEGF-D**

products for the treatment of neuropathologies. Alitalo, Kari; Karkkainen, Marika; Haiko, Paula; Sainio, Kirsi; Wartiovaara, Kirmo (Finland). U.S. Pat. Appl. Publ. US 20040214766 A1 20041028, 125 pp., Cont.-in-part of U.S. Ser. No. 262,538. (English). CODEN: USXXCO. APPLICATION: US 2003-669176 20030923. PRIORITY: US 2001-PV326326 20011001; US 2002-262538 20020930.

AB The present invention relates to VEGF-C or **VEGF-D** materials and methods for promoting growth and differentiation of neural stem cells and materials and methods for administering said cells to inhibit neuropathol.

L13 ANSWER 2 OF 12 MEDLINE on STN

DUPLICATE 1

2004140625. PubMed ID: 15032727. Development of vascular endothelial growth factor receptor (VEGFR) kinase inhibitors as anti-angiogenic agents in cancer therapy. Underiner T L; Ruggeri B; Gingrich D E. (Departments of Chemistry and Oncology, Cephalon, Inc, West Chester, PA, USA.. tunderin@cephalon.com) . Current medicinal chemistry, (2004 Mar) 11 (6) 731-45. Ref: 106. Journal code: 9440157. ISSN: 0929-8673. Pub. country: Netherlands. Language: English.

AB Among the known angiogenic growth factors and cytokines implicated in the modulation of normal and pathological angiogenesis, the VEGF family (VEGF-A, VEGF-B, VEGF-C, **VEGF-D**) and their corresponding receptor tyrosine kinases [VEGFR-1 (Flt-1), VEGFR-2 (Flk-1, KDR), and VEGFR-3 (Flt-4)] play a paramount and indispensable role in regulating the multiple facets of the angiogenic and lymphangiogenic processes, as well as the induction of vascular permeability and inflammation. The receptor VEGFR-2/KDR is the principal one through which VEGFs exert their mitogenic, chemotactic, and vascular permeabilizing effects on the host vasculature. Increased expression of VEGFs by tumor cells and VEGFR-2/KDR and VEGFR-1/Flt-1 by the tumor-associated vasculature are a hallmark of a variety of human and rodent tumors in vivo and correlates with tumor growth rate, micro-vessel density/proliferation, tumor metastatic potential, and poorer patient prognosis in a variety of malignancies. Approaches to disrupting the VEGF/VEGFR signaling cascade range from biological agents (soluble receptors, anti-VEGF and anti-VEGFR-2 antibodies, and VEGF transcription inhibitors) to small molecule ATP competitive VEGFR inhibitors. Examples from this latter class that are currently in clinical development include compounds from distinct chemical classes such as: indolin-2-ones, anilinoquinazolines, anilinophthalazines, isothiazoles, indolo- and indenocarbazoles. The structure activity relationships, biochemical and pharmacological profile of optimized representatives from each of these classes constitute the subject matter of this review.

L13 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2004:210013 Document No.: PREV200400212426. Quantification of vascular endothelial growth factor-C (VEGF-C) by a novel ELISA. Weich, Herbert A. [Reprint Author]; Bando, Hiroko; Brokelmann, Maren; Baumann, Petra; Toi, Masakazu; Barleon, Bernhard; Alitalo, Kari; Sipos, Bence; Sleeman, Jonathan. Department RDIF, GBF, Mascheroder Weg 1, D-38124, Braunschweig, Germany. weich@gbf.de. Journal of Immunological Methods, (15 February 2004) Vol. 285, No. 2, pp. 145-155. print. ISSN: 0022-1759 (ISSN print). Language: English.

AB Lymphangiogenesis plays an important role in several normal and pathological conditions such as wound healing, inflammation or metastasis formation in several malignancies. VEGF-C and **VEGF-D** are important and specific regulatory factors for lymphatic endothelial proliferation and lymphangiogenesis. In order to develop a highly sensitive and specific detection system for VEGF-C, we produced soluble binding proteins and antibodies for a microtiterplate-based assay. Here we describe a specific enzyme-linked immunosorbent assay (ELISA) for the measurement of human, rat and murine VEGF-C. The

different **antibodies** developed against human and rat VEGF-C could be combined to detect processed and partially processed VEGF-C in a specific way. The ELISA was able to detect human and rat VEGF-C with a minimum detection limit of 100 pg/ml. The assay did not show any cross-reactivity with the related protein **VEGF-D**. Furthermore, complex formation with its soluble receptors VEGFR-2 and VEGFR-3 did not restricted the sensitivity of the assay. Using this assay, VEGF-C was measured in supernatants and lysates of different cell types and in tumour tissue samples of murine, rat and human origin. Cell lines secrete VEGF-C in very low amounts (<1 ng/ml) whereas VEGF-C transfected cells can secrete up to 50 ng/ml VEGF-C into the supernatant. In human tumour tissue samples VEGF-C was detected in some carcinomas in the low protein range. This ELISA will be a useful tool for investigations concerning the physiological function of VEGF-C in lymphangiogenesis under normal and pathophysiological conditions.

L13 ANSWER 4 OF 12 MEDLINE on STN
2003312109. PubMed ID: 12839674. Expression of vascular endothelial growth factor (VEGF) C and VEGF receptor 3 in non-small cell lung cancer. Dong Xin; Qiu Xue-shan; Wang En-hua; Li Qing-chang; Gu Wei. (Department of Pathology, China Medical University, Shenyang 110001, China.) Zhonghua bing li xue za zhi Chinese journal of pathology, (2003 Apr) 32 (2) 128-32. Journal code: 0005331. ISSN: 0529-5807. Pub. country: China. Language: Chinese.

AB OBJECTIVE: To study the relationship between angiogenesis and lymphangiogenesis with the expression of vascular endothelial growth factor C (VEGF-C) and VEGFR-3 in human non-small cell lung cancer (NSCLC). METHODS: Samples of 76 NSCLC cases with the neighboring noncancerous tissue were studied using **anti- VEGF-C**, VEGFR-3 and CD34 **antibodies**. Assessment of lymphatic vessel density and microvessel density (MVD) were performed. RESULTS: VEGF-C expression in NSCLC was associating with the differentiation of tumor cells ($P = 0.009$). Expression of VEGF-C and VEGFR-3 was significantly associated with lymph node metastasis ($P = 0.008$ and $P = 0.013$ respectively) and lymphatic invasion ($P = 0.027$ and $P = 0.020$ respectively). A significant positive correlation was found between VEGF-C in cancer cells and VEGFR-3 in lymphatic endothelial cells ($P = 0.009$). The number of lymphatic vessels ($P = 0.006$) and microvascular ($P = 0.046$) in VEGF-C positive tumors was significantly larger than in VEGF-C-negative tumors. Lymphatic vessel density was closely related to lymph node metastasis ($P = 0.010$), lymphatic invasion ($P = 0.019$) and clinical stages ($P = 0.015$). MVD was closely related to blood metastasis ($P < 0.001$) and clinical stages ($P < 0.001$). Patients with positive VEGF-C expression had a worse prognosis than those with a negative VEGF-C expression ($P < 0.001$). CONCLUSIONS: VEGF-C/**VEGF-D** in NSCLCs, are related to lymphangiogenesis and angiogenesis, as well as to the occurrence and the development of lung cancers. VEGF-C promotes intratumoral lymphangiogenesis via VEGFR-3, resulting facilitated invasion of cancer cells into the lymphatic vessels. VEGF-C expression can be a useful predictor of poor prognosis in NSCLC.

L13 ANSWER 5 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
2002:334517 Document No.: PREV200200334517. **Antibodies** to truncated **VEGF-D** and thereof. Achen, Marc G. [Inventor, Reprint author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 May 07, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. <http://www.uspto.gov/web/menu/patdata.html>. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The invention is based on the isolation of **antibodies** that were made to a polypeptide having the amino acid sequence for a truncated **VEGF-D**. One of these **antibodies** can interfere with the activity of **VEGF-D** mediated by VEGFR-2 and

interfere with the binding of **VEGF-D** to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these **antibodies**.

L13 ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:15527 Document No.: PREV200300015527. Role of VEGF family members and receptors in coronary vessel formation. Tomanek, Robert J. [Reprint Author]; Holifield, Jennifer S.; Reiter, Rebecca S.; Sandra, Alexander; Lin, Jim J.-C.. Department of Anatomy and Cell Biology, University of Iowa, 1-402 Bowen Science Bldg., Iowa City, IA, 52242, USA. robert-tomanek@uiowa.edu. Developmental Dynamics, (November 2002) Vol. 225, No. 3, pp. 233-240. print. ISSN: 1058-8388 (ISSN print). Language: English.

AB The specific roles of vascular endothelial growth factor (VEGF) family members and their receptors (VEGFRs) in coronary vessel formation were studied. By using the quail heart explant model, we found that neutralizing **antibodies** to VEGF-B or VEGF-C inhibited tube formation on the collagen gel more than **anti-VEGF-A**. Soluble VEGFR-1, a receptor for VEGF-A and -B, inhibited tube formation by 87%, a finding consistent with that of VEGF-B inhibition. In contrast, addition of soluble VEGFR-2, a receptor for VEGF family members A, C, D, and E, inhibited tube formation by only 43%. Acidic FGF-induced tube formation dependency on VEGF was demonstrated by the attenuating effect of a soluble VEGFR-1 and -2 chimera. The localization of VEGF R-2 and R-3 was demonstrated by in situ hybridization of serial sections, which documented marked accumulations of transcripts for both receptors at the base of the truncus arteriosus coinciding with the temporal and spatial formation of the coronary arteries by means of ingrowth of capillary plexuses. This finding suggests that both VEGFR-2 and R-3 may play a role in the formation of the coronary artery roots. In summary, these experiments document a role for multiple members of the VEGF family and their receptors in formation of the coronary vascular bed.

L13 ANSWER 7 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:154373 Document No.: PREV200300154373. Expression of Vascular Endothelial Growth Factors, Vegf-B, Vegf-C, **Vegf-D**, and of VegfC Receptors, Flt-4 (VEGFR-3) in Inflamed and Vascularized Human Corneas. Philipp, W. E. [Reprint Author]; Speicher, L. [Reprint Author]. Department of Ophthalmology, University of Innsbruck, Innsbruck, Austria. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 1755. cd-rom. Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002. Language: English.

AB Purpose: Vascular endothelial growth factors are key modulators of vasculogenesis and angiogenesis. VEGF-B, VEGF-C, and **VEGF-D** are newly discovered growth factors that show close homology to VEGF. Since VEGF and its receptors Flt-1 and Flk-1 are strongly expressed in vascularized corneas, we investigated the expression of VEGF-B, C, D, and of VEGF-C receptor, Flt-4 (VEGFR-3), in inflamed and vascularized human corneas to help define a possible role of these cytokines in the pathogenesis of corneal neovascularization. Methods: 26 vascularized human corneas were obtained at the time of penetrating keratoplasty in patients with various inflammatory corneal diseases. Immunohistochemistry was performed on frozen sections using the streptavidin-biotin-peroxidase method and **antibodies** against VEGF-B, C, D, Flt-4, and against von Willebrand's factor to confirm the presence of neovascularization. Results: While only weak immunostaining for VEGF-B and VEGF-C was found on superficial corneal epithelial cells, all epithelial layers strongly stained with **anti-VEGF-D antibody** in corneas with chemical burns, herpetic stromal keratitis, atopic keratitis, zoster keratitis, fungal keratitis, and chronic allograft

rejection. Flt-4 was strongly expressed on endothelial cells of limbal vessels, of newly formed vessels in the stroma, and interestingly, moderately on corneal endothelial cells. Conclusions: These results demonstrate that VEGF-D, and to a lesser extent also VEGF-B, VEGF-C, and VEGFR-3 are expressed in inflamed and vascularized human corneas and may play a role in the pathogenesis of corneal neovascularization.

L13 ANSWER 8 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2001:112744 Document No.: PREV200100112744. VEGF-D

promotes the metastatic spread of tumor cells via the lymphatics. Stacker, Steven A. [Reprint author]; Caesar, Carol; Baldwin, Megan E.; Thornton, Gillian E.; Williams, Richard A.; Prevo, Remko; Jackson, David G.; Nishikawa, Shin-Ichi; Kubo, Hajime; Achen, Marc G.. Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Melbourne, VIC, Australia. steven.stacker@ludwig.edu.au. Nature Medicine, (February, 2001) Vol. 7, No. 2, pp. 186-191. print. ISSN: 1078-8956. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (VEGF)-D, a ligand for the lymphatic growth factor receptor VEGFR-3/Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that VEGF-D induced the formation of lymphatics within tumors. Moreover, expression of VEGF-D in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. VEGF-D also promoted tumor angiogenesis and growth. Lymphatic spread induced by VEGF-D could be blocked with an antibody specific for VEGF-D. This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L13 ANSWER 9 OF 12 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2001:255208 Document No.: PREV200100255208. Vascular endothelial growth factor-D (VEGF-D) is an endothelial hyperpermeability

inducing growth factor differentially expressed in human cardiac allografts. Wong, D. [Reprint author]; Luckhurst, J. [Reprint author]; Toma, H. [Reprint author]; Kuipers, N. [Reprint author]; Loo, S. [Reprint author]; Suarez, A. [Reprint author]; Wilson, J. E. [Reprint author]; McManus, B. M. [Reprint author]. University of British Columbia - St. Paul's Hospital, Vancouver, BC, Canada. Journal of Heart and Lung Transplantation, (February, 2001) Vol. 20, No. 2, pp. 156. print. Meeting Info.: Twenty-First Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation. Vancouver, Canada. April 25-28, 2001. International Society for Heart and Lung Transplantation. ISSN: 1053-2498. Language: English.

L13 ANSWER 10 OF 12 MEDLINE on STN

DUPLICATE 2

2001156199. PubMed ID: 11180159. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumour angiogenesis. Achen M G; Williams R A; Minekus M P; Thornton G E; Stenvers K; Rogers P A; Lederman F; Roufail S; Stacker S-A. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . Journal of pathology, (2001 Feb) 193 (2) 147-54. Journal code: 0204634. ISSN: 0022-3417. Pub. country: England: United Kingdom. Language: English.

AB Expression of angiogenic and lymphangiogenic factors by tumours may influence the route of metastatic spread. Vascular endothelial growth

factor (VEGF) is a regulator of tumour angiogenesis, but studies of the inhibition of solid tumour growth by neutralizing **anti-VEGF antibodies** indicated that other angiogenic factors may be involved. **VEGF-D** may be an alternative regulator because like VEGF it is angiogenic and it activates VEGF receptor-2 (VEGFR-2), an endothelial cell receptor which is a key signalling molecule in tumour angiogenesis. This study reports the generation of monoclonal **antibodies** to the receptor-binding domain of **VEGF-D** and the use of these **antibodies** to localize **VEGF-D** in malignant melanoma. **VEGF-D** was detected in tumour cells and in vessels adjacent to immunopositive tumour cells, but not in vessels distant from the tumours. These findings are consistent with a model in which **VEGF-D**, secreted by tumour cells, activates endothelial cell receptors and thereby contributes to the regulation of tumour angiogenesis and possibly lymphangiogenesis. In addition, **VEGF-D** was detected in the vascular smooth muscle, but not the endothelium, of vessels in adult colon. The endothelium of these vessels was negative for VEGFR-2 and VEGFR-3. As VEGF receptors can be up-regulated on endothelium in response to vessel damage and ischaemia, these findings of a specific localization of **VEGF-D** in smooth muscle of the blood vessels suggest that **VEGF-D** produced by vascular smooth muscle could play a role in vascular repair by stimulating the proliferation of endothelial cells.

L13 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2004 ACS on STN
2000:742365 Document No. 133:291559 Methods for diagnosis and treatment of metastatic prostate tumors based on flt-4 expression and ligand binding. Su, Sai L. (Northwest Biotherapeutics, Inc., USA). PCT Int. Appl. WO 2000062063 A1 20001019, 78 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US8079 19990413.

AB The present invention is directed to methods for the identification of a prostate cancer cell that has metastatic potential or a cell that is or is derived from a secondary prostate tumor metastasis by screening for the expression of flt-4, the cellular receptor of vascular endothelial growth factor-C and -D ("**VEGF-C**", "**VEGF-D**"). The present invention is also directed to methods for treating, inhibiting or preventing secondary prostate tumor metastases by inhibiting the expression or activity of flt-4, e.g., inhibiting flt-4:VEGF-C/D complex formation (binding), by administration of a therapeutic agent. Compsns. useful in such methods are also provided.

L13 ANSWER 12 OF 12 MEDLINE on STN DUPLICATE 3
2000247148. PubMed ID: 10785369. Monoclonal **antibodies** to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. **VEGF-D** consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human **VEGF-D** in order to generate **VEGF-D** antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed **VEGF-**

D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature **VEGF-D** for binding to both VEGFR-2 and VEGFR-3 for binding to mature **VEGF-D**. This indicates that the binding epitopes on **VEGF-D** for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to **VEGF-D**. The **anti-(VEGF-D)** mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of **VEGF-D**

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=> s "VEGF-D"
L14          791 "VEGF-D"
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=> s l14 and brain tumor
L15          10 L14 AND BRAIN TUMOR
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=> dup remove l15
PROCESSING COMPLETED FOR L15
L16          3 DUP REMOVE L15 (7 DUPLICATES REMOVED)
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=> d l16 1-3 cbib abs
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L16 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN 2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of **brain tumors**. Debinski, Waldemar [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences. Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH). ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L16 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1 2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of **brain tumors**. Debinski Waldemar; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable **brain tumors**. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA,

a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of **brain tumors**. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of **brain tumors** or for monitoring their progression following initial treatment.

L16 ANSWER 3 OF 3 MEDLINE on STN

DUPLICATE 2

2002052394. PubMed ID: 11778649. VEGF-D is an

X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating **brain tumor** of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (VEGF-D), is the newest mammalian member of VEGF family. We analyzed VEGF-D in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of VEGF-D, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously VEGF-D, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced VEGF-D expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and VEGF-D levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because VEGF-D activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The VEGF-D system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

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(FILE 'HOME' ENTERED AT 19:28:24 ON 17 NOV 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 19:28:33 ON 17 NOV 2004

L1 3562 S DETECTION ASSAY

L2 0 S L1 AND VEGF-D ANTIBODY
 L3 865 S L1 AND ANTIBODY
 L4 0 S L3 AND VEGF-D
 L5 0 S L3 AND VEGF
 L6 0 S L1 AND ANTI-VEGF
 L7 2622989 S ANTIBOD?
 L8 150 S L7 AND VEGF-D
 L9 60 S L8 AND CANCER
 L10 8 S L9 AND BRAIN
 L11 5 DUP REMOVE L10 (3 DUPLICATES REMOVED)
 L12 23 S L8 AND ANTI-VEGF
 L13 12 DUP REMOVE L12 (11 DUPLICATES REMOVED)
 L14 791 S "VEGF-D"
 L15 10 S L14 AND BRAIN TUMOR
 L16 3 DUP REMOVE L15 (7 DUPLICATES REMOVED)

=> s l14 and brain

L17 27 L14 AND BRAIN

=> dup remove l17

PROCESSING COMPLETED FOR L17

L18 20 DUP REMOVE L17 (7 DUPLICATES REMOVED)

=> d l18 1-20 cbib abs

L18 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2004:905599 Methods for the use of VEGF-C or VEGF-D
 products for the treatment of neuropathologies. Alitalo, Kari;
 Karkkainen, Marika; Haiko, Paula; Sainio, Kirsi; Wartiovaara, Kirmo
 (Finland). U.S. Pat. Appl. Publ. US 20040214766 A1 20041028, 125 pp.,
 Cont.-in-part of U.S. Ser. No. 262,538. (English). CODEN: USXXCO.
 APPLICATION: US 2003-669176 20030923. PRIORITY: US 2001-PV326326
 20011001; US 2002-262538 20020930.

AB The present invention relates to VEGF-C or VEGF-D
 materials and methods for promoting growth and differentiation of neural
 stem cells and materials and methods for administering said cells to
 inhibit neuropathol.

L18 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2003:242181 Document No. 138:266043 Treatment of central nervous system
 disorders by use of PDGF or VEGF. Delfani, Kioumars; Janson, Ann Marie;
 Kuhn, Georg H.; Plate, Karlheinz; Schanzer, Anne; Wachs, Frank-Peter;
 Zhao, Ming (Neuronova AB, Swed.). PCT Int. Appl. WO 2003024478 A1
 20030327, 119 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA,
 BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
 ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
 KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ,
 OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH,
 CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE,
 NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO
 2002-IB3998 20020919. PRIORITY: US 2001-PV323381 20010919; US
 2001-PV326044 20010928.

AB The invention relates generally to methods of influencing central nervous
 system cells to produce progeny useful in the treatment of CNS disorders.
 More specifically, the invention includes methods of exposing a patient
 suffering from such a disorder to a reagent that modulates the
 proliferation, migration, differentiation and survival of central nervous
 system cells. These methods are useful for reducing at least one symptom
 of the disorder. The reagent used is platelet-derived growth factor
 (PDGF), vascular endothelial growth factor (VEGF), a combination of both,
 a PDGF agonist or a VEGF agonist. Methods for the modulation of VEGF and
 PDGF receptors with antibodies are also claimed, as well as methods for
 the screening of PDGF and VEGF agonist in a non-human mammal.

L18 ANSWER 3 OF 20 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of **brain** tumors. Debinski, Waldemar [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110; Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences. Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH). ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L18 ANSWER 4 OF 20 MEDLINE on STN DUPLICATE 1

2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of **brain** tumors. Debinski Waldemar; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

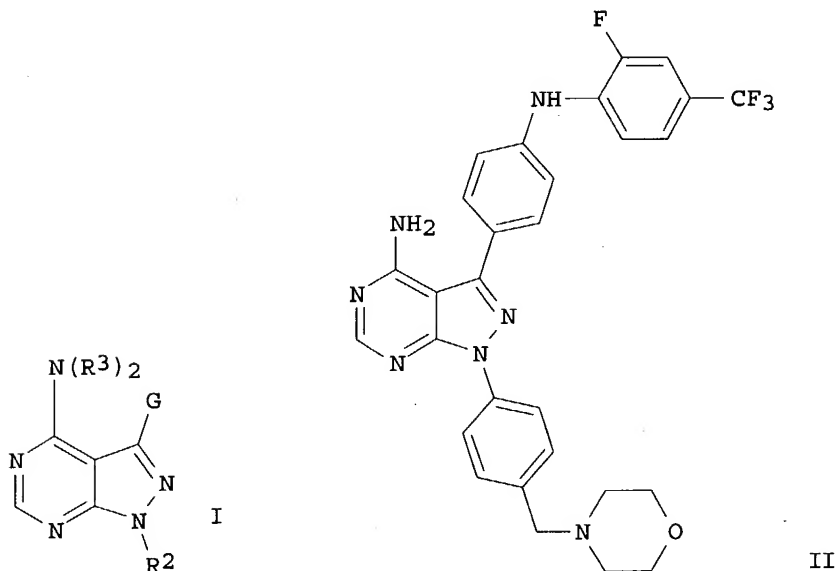
AB Human high-grade astrocytomas (HGA) are the most prevalent incurable **brain** tumors. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of **brain** tumors. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of **brain** tumors or for monitoring their progression following initial treatment.

L18 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2002:793426 Document No. 137:310925 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott G.m.b.H. & Co. K.-G., Germany). PCT Int. Appl. WO 2002080926 A1 20021017, 867 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,

ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English).
 CODEN: PIXXD2. APPLICATION: WO 2002-US9104 20020322. PRIORITY: US 2001-815310 20010322.

GI

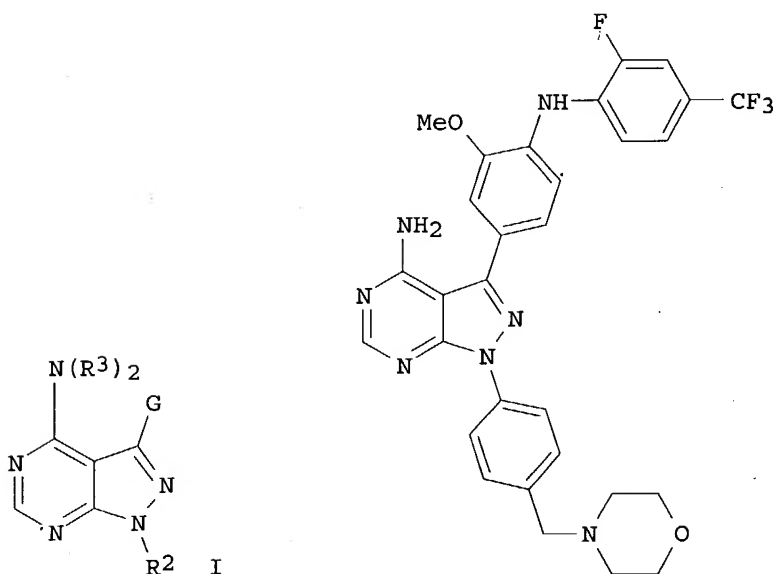


AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of $\leq 50 \mu\text{M}$. Certain compds. of the invention also significantly inhibited cdc2 or cellular VEGF-induced KDR tyrosine kinase phosphorylation at concns. of $\leq 50 \mu\text{M}$. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L18 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN
 2002:754390 Document No. 137:263056 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt;

Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M.
 (Abbott GmbH & Co. KG, Germany). PCT Int. Appl. WO 2002076986 A1
 20021003, 440 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA,
 BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
 ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
 KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ,
 OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM;
 RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB,
 GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English).
 CODEN: PIXXD2. APPLICATION: WO 2002-US8996 20020322. PRIORITY: US
 2001-PV278047 20010322.

GI



AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R_2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or $C_6H_4-4-CH_2E$; E = (un)substituted alkyl-OR, alkyl-CO₂R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR₂; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R_3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts.; optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh₃)₄, and Na₂CO₃ in H₂O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)₃BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of $\leq 50 \mu M$. Certain compds. of the invention also significantly inhibited cdc2 or cellular VEGF-induced KDR tyrosine kinase phosphorylation at concns. of $\leq 50 \mu M$. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L18 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2002:637486 Document No. 137:164115 **VEGF-D** expression in **brain** cancer in relation to diagnosis and treatment. Debinski, Waldemar; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB **VEGF-D** serves as a target for diagnosing and treating glioblastoma multiforme and related **brain** cancers. Cancer in a **brain** tissue sample is detected by analyzing expression of **VEGF-D** in the sample. **Brain** cancer is treated by modulating **VEGF-D** gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with **VEGF-D** binding to a **VEGF-D** receptor.

L18 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2002:594892 Document No. 137:150622 Cloning, tissue expression and therapeutic use of Flt4 (VEGFR-3) polypeptides, their polynucleotides, and antibodies in the diagnosis and treatment of cancer. Alitalo, Kari; Aprelikova, Olga; Pajusola, Katri; Armstrong, Elina; Korhonen, Jaana; Kaipainen, Arja (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2002060950 A2 20020808, 173 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US1784 20020122. PRIORITY: US 1994-340011 19941114; US 1994-169079 19941114; US 1997-901710 19970728; US 2001-765534 20010119.

AB The present invention provide purified Flt4 receptor tyrosine kinase polypeptides and fragments thereof, polynucleotides encoding such polypeptides, antibodies that specifically bind such polypeptides, and uses thereof in the treatment and diagnosis of disease, specifically cancer.

L18 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2002:555522 Document No. 137:119669 VEGFR-3 inhibitor materials and methods. Alitalo, Kari; Koivunen, Erkki; Kubo, Hajime (Ludwig Institute for Cancer Research, USA; Licentia Ltd.). PCT Int. Appl. WO 2002057299 A2 20020725, 149 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IB99 20020116. PRIORITY: US 2001-PV262476 20010117.

AB The present invention relates to the diagnostics, evaluation, and therapeutic intervention of disorders mediated by the activity of cell surface receptor VEGFR-3, which activity often is stimulated by VEGFR-3 ligands VEGF-C and **VEGF-D**. More particularly, the present invention identifies novel methods and compns. for the inhibition of VEGF-C/D binding to VEGFR-3. The compns. of the present invention will

be useful the inhibition of angiogenesis and lymphangiogenesis. Many uses of such compds., for screening samples, imaging, diagnosis, and therapy, are also provided. For example, in one embodiment, the invention provides an isolated peptide comprising the formula: X1X2X3X4X5X6X7X8, wherein X1 through X8 are amino acid residues.

L18 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

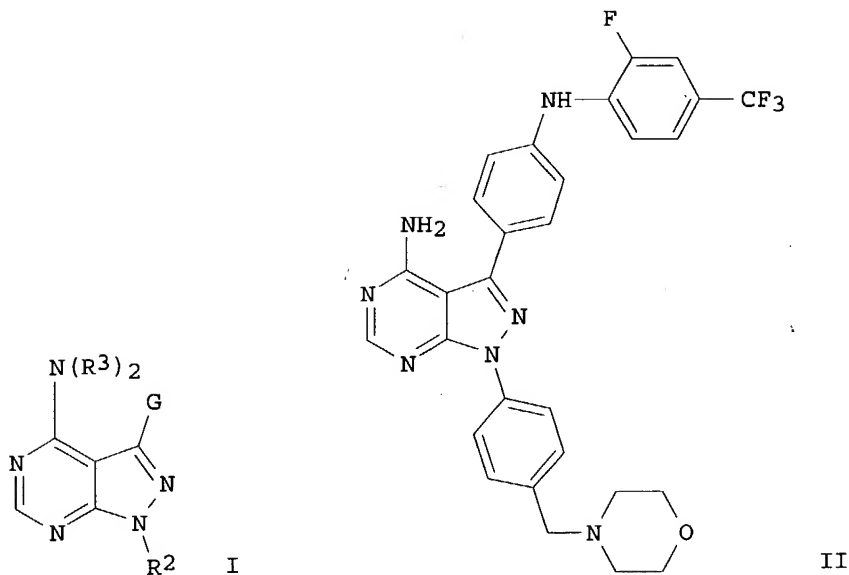
2002:391912 Document No. 137:1836 Measurement of DNA methylation for analysis of the toxicology of substances. Olek, Alexander; Piepenbrock, Christian; Berlin, Kurt (Epigenomics Ag, Germany). PCT Int. Appl. WO 2002040710 A2 20020523, 113 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2001-EP12951 20011108. PRIORITY: DE 2000-10056802 20001114.

AB The invention relates to a method for anal. of the toxicol. of a substance by measuring its effects using changes in DNA methylation as an indicator of toxicol. According to the invention, a DNA sample is taken from an organism or a cell culture which has been exposed to a specific substance which is to be examined on account of its toxicol. effect. The DNA contained in said sample is chemical pre-treated and the base sequence of a section of the modified DNA is determined. The preferred method is to convert cytosine in CpG dinucleotides to uracil using bisulfite. Probes specific for cytosine- or uracil-containing DNA can be used to detect changes in methylation. From there, a characteristic methylation state or a characteristic methylation model is determined for the sample. By comparison with data from methylation states of other samples, the effect of a substance on the organism or the cell culture is determined and/or compared to other substances in toxicol. terms. A panel of sequences that can be used to analyze the effects of poisons is described.

L18 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2002:814851 Document No. 137:310930 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott Laboratories, USA). U.S. Pat. Appl. Publ. US 2002156081 A1 20021024, 426 pp., Cont.-in-part of U.S. Ser. No. 663,780. (English). CODEN: USXXCO. APPLICATION: US 2001-815310 20010322. PRIORITY: US 1999-PV154620 19990917; US 2000-663780 20000915.

GI



AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared. For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of $\leq 50 \mu\text{M}$. Certain compds. of the invention also significantly inhibited cdc2 or cellular VEGF-induced KDR tyrosine kinase phosphorylation at concns. of $\leq 50 \mu\text{M}$. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L18 ANSWER 12 OF 20 CAPLUS -COPYRIGHT 2004 ACS on STN

2002:72748 Document No. 136:146104 Human stress genes identified using DNA microarrays. Chenchik, Alex; Lukashev, Matvey E. (Clontech, USA). U.S. Pat. Appl. Publ. US 2002009730 A1 20020124, 57 pp., Cont.-in-part of U.S. Ser. No. 441,920. (English). CODEN: USXXCO. APPLICATION: US 2001-782909 20010213. PRIORITY: US 1998-222256 19981228; US 1999-441920 19991117; US 1999-440305 19991117.

AB Human stress arrays and methods for their use are provided. The subject arrays include a plurality of polynucleotide spots, each of which is made up of a polynucleotide probe composition of unique polynucleotides corresponding to a human stress gene. The average length of the polynucleotide probes is between 50 to 1000 nucleotides. The d. of the spots on the array did not exceed 400/cm2 and the spots had a diameter ranging between 10 to 5000 μm . Furthermore, the number of polynucleotide probe spots on the array ranged between 50 to 2000 nucleotides. The subject arrays find use in hybridization assays, particularly in assays

for the identification of differential gene expression of human stress genes. 236 Different human stress genes were identified using this approach.

L18 ANSWER 13 OF 20 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation.
on STN

2002:42711 The Genuine Article (R) Number: 506AC. Expression of vascular endothelial growth factors and their receptors in and around intracranial arteriovenous malformations. Koizumi T (Reprint); Shiraishi T; Hagihara N; Tabuchi K; Hayashi T; Kawano T. 5-1-1 Nabeshima, Saga 8498501, Japan (Reprint); Saga Med Sch, Dept Neurosurg, Saga, Japan; St Marys Hosp, Dept Neurosurg, Kurume, Fukuoka, Japan; Fukuoka Tokushukai Med Ctr, Dept Neurosurg, Kasuga, Fukuoka, Japan. NEUROSURGERY (JAN 2002) Vol. 50, No. 1, pp. 117-124. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0148-396X. Pub. country: Japan. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB OBJECTIVE: The precise mechanisms responsible for the development and growth of intracranial arteriovenous malformations (AVMs) remain unclear, but it has been hypothesized that vascular endothelial growth factors (VEGFs) might be involved in their pathogenesis. The aim of this study was to examine immunohistochemically the presence of the VEGF family (VEGF-A to -D) and their receptors (Flt-1, Flk-1, and Flt-4) in the surgically resected AVM nidus.

METHODS: The AVM nidus was surgically obtained from 31 patients with AVMs (mean age, 40.5 yr, range 13-73 yr). The mean size of the nidus was 31.6 mm (range, 15-60 mm). Formalin-fixed, paraffin-embedded specimens were stained immunohistochemically by the labeled streptavidin-biotin method with antibodies against VEGF-A to -D, as well as Flt-1, Flk-1, and Flt-4.

RESULTS: Positive staining for VEGF-A to -D was observed in the endothelial cells of the abnormal vessels involved in the AVM nidus and in the cytoplasm of astroglia surrounding it. Samples from 30 (96.8%) of 31 patients stained positive for VEGF-A, 4 (9.7%) for VEGF-B, 17 (54.5%) for VEGF-C, and 16 (51.6%) for VEGF-D. Flt-1, Flk-1, and Flt-4 were also positive chiefly, but not exclusively, in the cytoplasm of vascular endothelium and smooth muscle cells of the vascular wall. With regard to VEGF receptors, it was found that among the 31 patients studied, 19 (61.3%) were immunohistochemically positive for Flt-1, 6 (19.4%) for Flk-1, and 19 (61.3%) for Flt-4. A comparison of mean nidus size and average age at operation revealed significant differences between patients positive for VEGF-C, VEGF-D, Flt-1, or Flt-4. In contrast, there were no significant differences in nidus size and age in patients positive for VEGF-A, VEGF-B, and Flk-1.

CONCLUSION: These results strongly suggest a possible contribution of the VEGF-VEGF receptor system to the growth of intracranial AVMs.

L18 ANSWER 14 OF 20 MEDLINE on STN

2003109214. PubMed ID: 12622137. Histone deacetylase inhibitors such as sodium butyrate and trichostatin A inhibit vascular endothelial growth factor (VEGF) secretion from human glioblastoma cells. Sawa Hiroki; Murakami Hiromi; Ohshima Yuko; Murakami Masahiro; Yamazaki Ichiro; Tamura Yasuo; Mima Tatsuo; Satone Akira; Ide Wataru; Hashimoto Ikuo; Kamada Hajime. (Oncology Research Center, Hokuto Hospital, Kisen 7-5, Inada-cho, Obihiro, Hokkaido 080-0833, Japan.. sawa@hokuto7.or.jp) . Brain tumor pathology, (2002) 19 (2) 77-81. Journal code: 9716507. ISSN: 1433-7398. Pub. country: Japan. Language: English.

AB We investigated the effects of histone deacetylase (HDAC) inhibitors such as sodium butyrate (SB) and trichostatin A (TSA) on the expression of vascular endothelial growth factor (VEGF) by human glioblastoma T98G, U251MG, and U87MG cells. The glioblastoma cells secreted three VEGF isoforms, VEGF (189), (165), and (121), although the expression levels of VEGF differed between the cell types. Treatment with either 5mM SB or 100 ng/ml TSA reduced VEGF secretion in conditioned media and reduced VEGF mRNA expression. We also studied the expression of VEGF-B, -C, and -D

mRNA in human glioblastoma cells and their modulation by HDAC inhibitors. The PCR products of VEGF-B (357bp), VEGF-C (501bp), and VEGF-D (484bp) were amplified in all glioblastoma cells examined. Treatment with SB reduced the expression of VEGF-D mRNA in U251MG cells and the expression of VEGF-B mRNA in U87MG cells. TSA treatment reduced the expression of VEGF-D in U251MG cells. These results suggest that HDAC inhibitors reduce VEGF secretion and modulate the expression of the other VEGF family members, and therefore may inhibit angiogenesis in glioblastoma tissues.

L18 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2001:545508 Document No. 135:132464 Cyclic peptide inhibitors of VEGF, VEGF-C, and VEGF-D, preparation methods, pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides monomeric monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of VEGF-D, as well as methods of making them, pharmaceutical compns. containing them, and therapeutic methods of use.

L18 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

2001:265459 Document No. 134:290751 Recombinant single-chain receptor antagonist proteins and their use in treatment of inflammatory disorders. Halkier, Torben; Schambye, Hans Thalsgard; Okkels, Jens Sigurd; Andersen, Kim Vilbour; Nissen, Torben Lauesgaard; Soni, Bobby; Jeppesen, Claus Bekker; Van Den Hazel, Bart (Maxygen Aps, Den.). PCT Int. Appl. WO 2001025277 A1 20010412, 123 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-DK563 20001006. PRIORITY: DK 1999-1438 19991007; DK 1999-1855 19991223; DK 2000-1119 20000720.

AB The invention relates to a single-chain oligomeric protein antagonist which binds to an extracellular ligand-binding domain of a cellular receptor of a type requiring binding of an oligomeric ligand to two or more receptor subunits to be activated, the protein comprising at least two, typically structurally homologous, receptor-binding sites of which at least one is capable of binding to a ligand-binding domain of the cellular receptor and at least one is incapable of effectively binding to a ligand-binding domain of the cellular receptor, whereby the single-chain oligomeric protein is capable of binding to the receptor, but incapable of activating the receptor; as well as to nucleotide sequences encoding such single-chain oligomeric proteins, expression vectors comprising such a nucleotide sequence, recombinant host cells comprising such a nucleotide sequence or expression vector, methods for producing the nucleotide sequences and proteins, pharmaceutical compns. comprising the single-chain oligomeric protein, and use of the single-chain oligomeric protein for the production of medicaments and in therapy. A preferred single-chain antagonist according to the invention is a TNF- α antagonist. Thus, a single-chain TNF- α protein comprising of 3 human TNF- α chains

connected by linker peptides was produced with *Saccharomyces cerevisiae* and shown to be an agonist of the TNF- α receptor. The same TNF- α trimer containing Y87R mutations in the first and third copies of TNF- α was also prepared. This was shown to be a partial TNF- α agonist and a competitive antagonist of the TNF- α receptor.

- L18 ANSWER 17 OF 20 MEDLINE on STN DUPLICATE 2
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.
- AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating **brain** tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant **brain** and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal **brain** and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

- L18 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN
2000:756544 Document No. 133:291568 Angiogenic growth factors for treatment of peripheral neuropathy. Isner, Jeffrey M. (St. Elizabeth's Medical Center, Inc., USA). PCT Int. Appl. WO 2000062798 A2 20001026, 63 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US9765 20000411. PRIORITY: US 1999-PV129768 19990415.
- AB A method for treating peripheral neuropathy, particularly ischemic peripheral neuropathy, is provided. The method involves administering to subjects in need of such treatment an effective amount of an angiogenic growth factor to alleviate a symptom of the neuropathy.

- L18 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN
2000:807534 Document No. 134:235274 Serum levels of vascular endothelial growth factor dependent on the stage progression of lung cancer. Matsuyama, Wataru; Hashiguchi, Teruto; Mizoguchi, Akira; Iwami, Fumiyuki; Kawabata, Masaharu; Arimura, Kimiyoshi; Osame, Mitsuhiro (Third Department of Internal Medicine, Kagoshima University School of Medicine, Kagoshima City, 890-8520, Japan). Chest, 118(4), 948-951 (English) 2000. CODEN:

CHETBF. ISSN: 0012-3692. Publisher: American College of Chest Physicians.

AB In lung cancer, vascular endothelial growth factor (VEGF), is an important cytokine and is correlated with tumor vessel d., malignant pleural effusions, and coagulation-fibrinolysis factors in vitro. We investigated the correlation between serum VEGF level and stage progression in lung cancer to study the predicted value of VEGF level. We also studied whether coagulation-fibrinolysis factors and Pao2 levels, which are also important factors for the prediction of the clin. course, are correlated with VEGF. Forty-nine patients with lung cancer were investigated prospectively. VEGF levels of sera and malignant effusions, and plasma concns. of coagulation-fibrinolysis factors were measured by ELISA. We measured Pao2 levels in all patients at rest. Serum levels of VEGF were increased significantly according to stage progression. Addnl., plasma concns. of D dimer, thrombin-antithrombin complex (TAT), and tissue plasminogen activator/plasminogen activator inhibitor type I complex were elevated significantly according to stage progression. The serum VEGF level had a significant pos. correlation with the TAT and D dimer levels. Serum VEGF levels had a significant neg. correlation with Pao2 levels. The incidence of cerebral vascular disorder was significantly higher in the patients with systemic hypoxemia than in those without ($p < 0.05$). Mean VEGF levels in malignant effusions in eight patients (five with pleural effusions, two with pericardial effusions, and one with both) were extremely high, especially in pericardial effusions ([mean \pm SD] pleural effusions, 531.9 ± 285.4 pg/mL; pericardial effusion, $3,071.6 \pm 81.3$ pg/mL). We predict that in lung cancer, VEGF production and the abnormality of the coagulation-fibrinolysis system differ depending on the stage of progression of disease. Serum VEGF levels would be affected by Pao2 levels in lung cancer.

L18 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2004 ACS on STN

1999:623899 Document No. 131:252571 Treatment of coronary and/or peripheral ischemia using an antithrombotic agent and an angiogenesis promoter. Barr, Eliav; Gould, Robert J.; Thomas, Kenneth A., Jr. (Merck and Co., Inc., USA). Brit. UK Pat. Appl. GB 2332373 A1 19990623, 39 pp. (English). CODEN: BAXXDU. APPLICATION: GB 1998-27279 19981211. PRIORITY: US 1997-68257 19971219; GB 1998-6705 19980327.

AB A method is provided for treating a patient having coronary and/or peripheral ischemic syndrome. The method involves administration to the patient of an effective amount of an antithrombotic agent, e.g. a glycoprotein IIb/IIIa antagonist, a thrombin inhibitor, a factor Xa inhibitor, or a low-mol.-weight heparin, and an effective amount of an angiogenesis promoter, e.g. a vascular endothelial growth factor or a fibroblast growth factor. Administration of the angiogenesis promoters may be by e.g. bolus injection, continuous i.v. administration, coated-stent implantation, and gene transfer, which provides localized or systemic delivery of the angiogenesis promoter at the ischemic tissue.

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L19 260 "VD1"

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L21 5 L20 AND VEGF-D

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L22 1 DUP REMOVE L21 (4 DUPLICATES REMOVED)

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L22 ANSWER 1 OF 1 MEDLINE on STN

DUPLICATE 1

2000247148. PubMed ID: 10785369. Monoclonal **antibodies** to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. **VEGF-D** consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human **VEGF-D** in order to generate **VEGF-D** antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed **VEGF-D**. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated **VD1**, is able to compete potently with mature **VEGF-D** for binding to both VEGFR-2 and VEGFR-3 for binding to mature **VEGF-D**. This indicates that the binding epitopes on **VEGF-D** for these two receptors may be in close proximity. Furthermore, **VD1** blocks the mitogenic response of human microvascular endothelial cells to **VEGF-D**. The anti-(**VEGF-D**) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of **VEGF-D**.

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L23 ANSWER 1 OF 15 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:380044 Document No.: PREV200300380044. LYMNAEA TRK, EXPRESSION IN DEVELOPMENT AND ADULTHOOD. Bulloch, A. G. [Reprint Author]; Diep, C. [Reprint Author]; Bulloch, E. S. [Reprint Author]; Hyslop, J.; Sossin, W.; Robbins, S.; Wildering, W. C. [Reprint Author]. Dept Physiol and Biophysics, Univ Calgary Hlth Sci Ctr, Calgary, AB, Canada. Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 822.6. <http://sfn.scholarone.com>. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience. Language: English.

AB The tyrosine kinase receptor, Lymnaea Trk (L-Trk), was cloned and characterized previously. These initial molecular studies showed that Ltrk is expressed in embryonic and juvenile stages, with limited expression in the adult. To investigate the cellular expression of Ltrk in more detail we generated rabbit polyclonal **antibodies** to two peptides designed from unconserved regions of the intracellular and extracellular domains of Ltrk. These antisera were then used for both immunocytochemistry and immunoprecipitation assays. We used a newly developed staged colony of Lymnaea to examine cellular expression patterns. Both sets of antisera showed three distinct patterns according to age: 1: uniform expression by all neurons in juvenile animals 1-2 months of age; 2: expression by **VD1**, RPD2 and a group of pedal

neurons in 3 month old animals, and 3: expression only by VD1 and RPD2 in animals 5-12 months old. The antisera generated against the "intracellular" peptide immunoprecipitated molecules of 90 and 140 kD that were recognised by an anti-phosphotyrosine **antibody**. These new antisera will therefore be valuable reagents in our continuing analysis of tyrosine kinases in Lymnaea.

L23 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 1
2002223976. PubMed ID: 11962096. [The role of gamma-delta T-lymphocyte subtypes in normal and pathologic conditions]. Rol' T-limfotsytiv subtypiv gamma-delta v normi ta pry patalohii. Dosenko V Ie; Goldenberg D I. (A.A. Bogomoletz National Medical University, Kiev.) Fiziolohichnyi zhurnal (Kiev, Ukraine : 1994), (2001) 47 (6) 71-84. Ref: 136. Journal code: 9601541. Pub. country: Ukraine. Language: Ukrainian.

AB In the review data about origin, spreading in the organism, differentiation, physiologic sense, role in diversity of pathologic processes, and also pharmaco- and immunocorrection's probable foundations of T-lymphocyte's new population with T cell receptor (TcR) gamma delta (TL gamma delta) are resumed. In the phylogenesis TL gamma delta are supposed to be older than T lymphocytes with TcR alpha beta. The conclusion is based upon domination of this lymphocyte population at gestation's early stage and huge representation of pseudogenes in the DNA region that encodes TcR structure of TL gamma delta. A morphological and functional resemblance of the given population with natural killer cells is underlined. It is paid attention to wide representation of TL gamma delta in the periphery tissues, poverty of TcR diapason that may evidence about postdifferentiation's process of TL gamma delta to be accomplished due to TcR genes rearrangement. This process appears to supply the enhancement of antigen-specific TL gamma delta in foreign agent's inculcation. A maturation process and probable mechanisms of these lymphocytes education in thymus is described. A classification of TL gamma delta depending on TcR structure and cytokine profile of the lymphocytes that subdivides them on T-helper/cytotoxic (Vg9/Vd2 phenotype) and cytotoxic/suppressor (Vd1 or Vd3 phenotype) was proposed. In the review the role of TL gamma delta in mucous immunity supporting and possible participating in systemic regulation of the immune response is emphasized. A physiologic role of TL gamma delta, namely ability to identify non-protein antigens (lipopolysaccharides, polyphosphates, glycolipids) and heat shock proteins, is also described. Evidences about uncertainty of incomplete phagocytosis phenomenon in vivo in case of TL gamma delta's normal function are given. Particularly it is made out that these lymphocytes are able to activate inducible NO-synthase in the macrophages that enhances their phagocytic activity in tens time. A function of these lymphocytes in defense against infection of bacterial, viral, protozoa, fungal origin, and also in tumor growth and autoimmune diseases is represented. Methods of specific therapeutic influence upon TL gamma delta, both pharmacological (pamidronat, 2,3-diphosphoglyceric acid) and immunologic profile (monoclonal **antibodies** conjugated with cytotoxic agent) are given.

L23 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2
2000247148. PubMed ID: 10785369. Monoclonal **antibodies** to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D

consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

L23 ANSWER 4 OF 15 MEDLINE on STN DUPLICATE 3
 1999059866. PubMed ID: 9841837. Analysis of the original antigenic sin **antibody** response to the major outer membrane protein of Chlamydia trachomatis. Berry J D; Peeling R W; Brunham R C. (Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada.) Journal of infectious diseases, (1999 Jan) 179 (1) 180-6. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB The anamnestic **antibody** response to the Chlamydia trachomatis major outer membrane protein (MOMP) was evaluated in mice after priming with serovar C and boosting either with the homologous serovar or with heterologous serovars (A, H, K, and B). Microimmunofluorescence **antibody** responses demonstrated that boosting with heterologous serovars strongly recalled **antibody** to serovar C, typical of an original antigenic sin (OAS) response. Boosting with serovars antigenically related to serovar C (A, H, and K) recalled **antibody** to the variable domain 1 (VD1) peptide of the MOMP of serovar C as determined by a pin-peptide ELISA. Complete amino acid substitution analysis of the VD1 peptide epitope of the MOMP showed that the original antigenic sin response to each boosting serovar contained **antibodies** with unique patterns of VD1 peptide recognition. The data suggest that antigenically related C. trachomatis serovars differentially recruit B cell lineages from a heterogeneous memory B cell pool that had been induced by priming with the original serovar and thus account for the OAS **antibody** response.

L23 ANSWER 5 OF 15 MEDLINE on STN DUPLICATE 4
 1998126215. PubMed ID: 9466739. Serotyping and genotyping of genital Chlamydia trachomatis isolates reveal variants of serovars Ba, G, and J as confirmed by omp1 nucleotide sequence analysis. Morre S A; Ossewaarde J M; Lan J; van Doornum G J; Walboomers J M; MacLaren D M; Meijer C J; van den Brule A J. (Department of Pathology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands.) Journal of clinical microbiology, (1998 Feb) 36 (2) 345-51. Journal code: 7505564. ISSN: 0095-1137. Pub. country: United States. Language: English.

AB Urogenital isolates (n = 93) of Chlamydia trachomatis were differentiated into serovars and variants by serotyping with monoclonal **antibodies** and genotyping by restriction fragment length polymorphism (RFLP) analysis of the PCR-amplified omp1 gene, respectively. The types of 87 of the 93 isolates (94%) were identical, as determined by both methods. Among these 87 isolates, 3 isolates were identified as the recently described new serovariant Ga/IOL-238 by omp1 nucleotide sequence analysis of the variable domains. Of the remaining six isolates, three isolates serotyped as both L2 and Ba but were identified as Ba/A-7 by genotyping by RFLP analysis of omp1. The omp1 nucleotide sequences of variable domains VD1, VD2, and VD4 of these urogenital Ba strains were identical to the sequences of the variable domains of Ba/J160, an ocular Ba type. The three remaining isolates were serotyped as J, but the patterns obtained by RFLP analysis of omp1, which were

identical for the three isolates, differed from that of prototype serovar J/UW36. *omp1* nucleotide sequence analysis revealed that these strains are genovariants of serovar J/UW36. Nucleotide sequence differences between serovar J/UW36 and this J genovariant, designated Jv, were found in both variable and constant domains. In conclusion, this study shows that the PCR-based genotyping of clinical *C. trachomatis* isolates by RFLP analysis of *omp1* has a higher discriminatory power and is more convenient than serotyping. Variants of *C. trachomatis* serovars Ba, G, and J were identified and characterized.

L23 ANSWER 6 OF 15 MEDLINE on STN DUPLICATE 5
 96333381. PubMed ID: 8757875. Characterization of the murine antibody response to peptides representing the variable domains of the major outer membrane protein of *Chlamydia pneumoniae*. Peterson E M; Cheng X; Qu Z; de La Maza L M. (University of California, Irvine 92717-4800, USA.) *Infection and immunity*, (1996 Aug) 64 (8) 3354-9. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB In an attempt to gain more knowledge about the immunogenicity of the variable domains (VDs) of the major outer membrane protein (MOMP) of *Chlamydia pneumoniae*, peptides representing these areas were used to immunize BALB/c and C57BL/6 mice. Antisera to the peptides and to peptides conjugated to keyhole limpet hemocyanin (KLH) were characterized by their ability to recognize the immunizing peptide and elementary bodies (EBs) of *C. pneumoniae* by enzyme-linked immunosorbent assay (ELISA) and Western blot (immunoblot). In addition, antiserum was analyzed for its molecular specificity by a pepscan as well as its in vitro neutralizing ability. In general, results obtained with antisera to the peptides paralleled the results obtained with the antisera to the KLH-conjugated peptides except that the titers or strength of reaction in the assays was less. Antisera to the VDs in both strains of mice gave ELISA titers to the homologous VD peptide ranging from 1,000 to >64,000. The strength of reactivity with the reduced MOMP as judged by Western blot, in most cases, paralleled the ELISA titer to the peptide. However, only antisera raised in both strains of mice to the VD1 and VD4 peptides reacted strongly with the EBs, suggesting surface exposure of these VDs. In addition, antisera to VD3 from C57BL/6 mice gave strong reactivity to EBs. By pepscan analysis antisera from both strains of mice reacted with several VD1 and VD3 octameric peptides, with weaker reactivity being seen with the octameric peptides in the other two VDs. This was in contrast to antisera raised to EBs of *C. pneumoniae* TW-183, which identified two immunogenic regions, one in VD1 and the other mapped to VD4. While antisera raised to EBs strongly neutralized the infectivity of *C. pneumoniae*, none of the peptide antisera was able to neutralize. In addition, peptides to the VDs were not able to block the neutralizing ability of the antisera to EBs of *C. pneumoniae*. Therefore, these results suggest that the VDs of the MOMP of *C. pneumoniae* are surface exposed but do not elicit neutralizing antibodies when linear peptides representing them are used as the immunogen.

L23 ANSWER 7 OF 15 MEDLINE on STN
 97084000. PubMed ID: 8930344. Identification and localization of a [Met5]-enkephalin-like peptide in the mollusc, *Lymnaea stagnalis*. Ewanger N M; Ridgway R L; Syed N I; Lukowiak K; Bulloch A G. (Department of Medical Physiology, University of Calgary, Alberta, Canada.) *Brain research*, (1996 Oct 21) 737 (1-2) 1-15. Journal code: 0045503. ISSN: 0006-8993. Pub. country: Netherlands. Language: English.

AB The goal of this study was to determine whether [Met5]-enkephalin, or an analog, is present in identified neurons in the central nervous system (CNS) of the freshwater snail, *Lymnaea stagnalis*. High performance liquid chromatography and radioimmunoassay of CNS tissue homogenates revealed both [Met5]-enkephalin and oxidized [Met5]-enkephalin. NO [Leu5]-enkephalin, [Met5]-enkephalin-Arg6-Phe7 or [Met5]-enkephalin-Arg6-Gly7-Leu8 were detected. Quantification of [Met5]-enkephalin, by radioimmunoassay, revealed that the *Lymnaea* CNS contains approximately 2.2

fmol/CNS (undigested tissue) and 4.5 fmol/CNS (tissue enzymatically digested with trypsin and carboxypeptidase B). The increased amount of [Met5]-enkephalin following tissue digestion indicates the presence of as yet unidentified extended forms of [Met5]-enkephalin in *Lymnaea*. Using indirect immunocytochemistry, a [Met5]-enkephalin-like peptide was localized to individual cells and cell clusters within the CNS, as well as to fibers in the atrium of the heart. A neuronal map depicting [Met5]-enkephalin-like immunoreactive cells was produced. Among the immunoreactive neurons were four identified, well-characterized, giant cells: VD1, RPD2, LB1 and RB1. Identifiable [Met5]-enkephalin-like immunoreactive neurons were characterized electrophysiologically and morphologically. Additionally, neurons VD1 and RPD2 were confirmed to be immunoreactive to *Lymnaea* alpha-peptide. The lack of both cross reactivity and sequence homology between alpha-peptide and [Met5]-enkephalin suggests that a [Met5]-enkephalin-like peptide and alpha-peptide are co-localized within these neurons.

- L23 ANSWER 8 OF 15 MEDLINE on STN DUPLICATE 6
 95239110. PubMed ID: 7536793. Fas and activation-induced Fas ligand mediate apoptosis of T cell hybridomas: inhibition of Fas ligand expression by retinoic acid and glucocorticoids. Yang Y; Mercep M; Ware C F; Ashwell J D. (Laboratory of Immune Cell Biology, National Institute of Health, Bethesda, Maryland 20892-1152, USA.) Journal of experimental medicine, (1995 May 1) 181 (5) 1673-82. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.
- AB Activation of T cell hybridomas induces a G1/S cell cycle block and apoptosis. We isolated a variant of the 2B4.11 T cell hybridoma that, when activated via the TCR, produced IL-2 and underwent growth inhibition but did not die. Analysis of a variety of cell surface molecules revealed that the variant cell line, termed VD1, expressed very low levels of Fas compared to the wild type cells. Unlike 2B4.11 cells, VD1 cells were not killed by Fas ligand (FasL)-bearing effector cells. To determine if Fas is involved in activation-induced apoptosis, two different reagents that specifically bind Fas without killing the T cell hybridomas, a monoclonal **antibody** and a soluble Fas:Fc chimeric molecule, were added to activated T cell hybridomas. Both treatments prevented activation-induced apoptosis in a dose-dependent manner, but had no effect on IL-2 production or growth inhibition. Northern blot analysis revealed that unactivated 2B4.11 cells expressed negligible levels of FasL mRNA, but transcripts were detectable as early as 2 h after activation and continued to increase up to 4-6 h after activation. Anti-TCR induced activation of 2B4.11 cells in the presence of a TCR- 2B4.11 variant resulted in death of the unactivated "bystander" cells, which was inhibited by anti-Fas **antibodies**. Finally, treatment of T hybridoma cells with 9-cis retinoic acid or glucocorticoids, which are known to prevent activation-induced T cell apoptosis, inhibited the up-regulation of FasL. We conclude that up-regulated expression of FasL and its subsequent interaction with Fas accounts for the apoptotic response of T cell hybridomas to activation, and that retinoic acid and corticosteroids inhibit activation-induced apoptosis by preventing up-regulation of FasL.

- L23 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
 1994:602745 Document No. 121:202745 Conformational mimicry of a chlamydial neutralization epitope on filamentous phage. Zhong, Guangming; Smith, George P.; Berry, Jody; Brunham, Robert C. (Div. Biological Sci., Univ. Missouri, Columbia, MO, 65211, USA). Journal of Biological Chemistry, 269(39), 24183-8 (English) 1994. CODEN: JBCHA3. ISSN: 0021-9258.
- AB Conformational constraints were imposed on a peptide epitope from *Chlamydia trachomatis* to improve its ability to elicit **antibodies** that cross-react with native antigen. Appropriate constraints were discovered by a strategy that required no prior knowledge of the epitope's native conformation. First, the authors constructed a library of 3.2+105 peptides in which the epitope's contact residues were

subject to random conformational constraints, each constrained peptide being fused genetically to the surface of a filamentous phage vector. Next, the authors selected phage displaying the most native-like peptides in the library by affinity purification with **antibodies** that bind the epitope only in its native conformation. Finally, the authors immunized mice with the selected phage and titered the resulting antisera against both whole cells and unconstrained peptide. The ratio of anti-cell titer to anti-peptide titer, which reflects the channeling of the **antibody** response to the native epitope, was up to five times higher for affinity-selected phage than for unselected peptide phage. In this case, therefore, "antigenic fitness," the ability of a peptide to bind **antibodies** specific for native epitope, correlated with "immunogenic fitness," its ability to elicit **antibodies** that are effective against the native antigen on an invading pathogen. If the correlation is general, surveying thousands or millions of peptides for antigenic fitness with phage display technol. may be a simple but effective pre-screen for immunogenic fitness, which is costly to assess directly.

- L23 ANSWER 10 OF 15 MEDLINE on STN DUPLICATE 7
 93373379. PubMed ID: 8364974. Neurons in a variety of molluscs react to **antibodies** raised against the VD1/RPD2 alpha-neuropeptide of the pond snail *Lymnaea stagnalis*. Kerkhoven R M; Ramkema M D; Van Minnen J; Croll R P; Pin T; Boer H H. (Department of Organismic Zoology, Faculty of Biology, Free University, Amsterdam, The Netherlands.) Cell and tissue research, (1993 Aug) 273 (2) 371-9. Journal code: 0417625. ISSN: 0302-766X. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
- AB The VD1 and RPD2 neurons of *Lymnaea stagnalis* innervate other central neurons, certain skin areas, the pneumostome area, and the auricle of the heart. Recently, a set of four (delta, epsilon, alpha, beta) neuropeptides produced by these giant neurons and by certain other central neurons has been characterized. Although alternative splicing of the preprohormone of these neurons yields at least 10 different alpha neuropeptides, an affinity-purified antiserum directed against a domain common to all alpha neuropeptides has previously been shown to be highly selective in staining VD1, RPD2 and other neurons that produce the preprohormone. Since the gene encoding the neuropeptides is structurally similar to that expressed in R15 of the marine opisthobranch *Aplysia californica*, we have used the affinity purified antiserum as a marker for VD1/RPD2-related systems in other molluscs. Immunopositive neurons and fibers are observed in the central nervous systems of all species studied (*Achatina fulica*, *Anodonta* sp., *Aplysia brasiliana*, *A. californica*, *Bulinus truncatus*, *Cepea* sp., *Eobania vermiculata*, *Helix aspersa*, *H. pomatia*, *Limax maximus*, *Mytilus edulis*, *Nassarius reticulatus*, *Viviparus viviparus*). Several medium-sized and small neurons and 1-4 giant neurons are found in the pulmonates and opisthobranchs. The giant neurons in pulmonates have locations in the subesophageal ganglion, axonal branching patterns, and terminal arborizations in the auricle of the heart; all these characteristics are similar to those of VD1 and RPD2. Double-labelling (Lucifer yellow injection, immunocytochemistry) confirms that the two giant neurons in *Helix pomatia* are Br and Br'. The immunoreactive cells in *A. fulica* appear to include the VIN and PON neurons. (ABSTRACT TRUNCATED AT 250 WORDS)

- L23 ANSWER 11 OF 15 MEDLINE on STN
 92240672. PubMed ID: 1315219. The VD1/RPD2 neuronal system in the central nervous system of the pond snail *Lymnaea stagnalis* studied by in situ hybridization and immunocytochemistry. Kerkhoven R M; Croll R P; Ramkema M D; Van Minnen J; Bogerd J; Boer H H. (Department of Organismic Zoology, Faculty of Biology, Amsterdam, The Netherlands.) Cell and tissue research, (1992 Mar) 267 (3) 551-9. Journal code: 0417625. ISSN: 0302-766X. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB VD1 and RPD2 are two giant neuropeptidergic neurons in the central nervous system (CNS) of the pond snail *Lymnaea stagnalis*. We wished to determine whether other central neurons in the CNS of *L. stagnalis* express the VD1/RPD2 gene. To this end, in situ hybridization with the cDNA probe of the VD1/RPD2 gene and immunocytochemistry with antisera specific to VD1 and RPD2 (the alpha 1-antiserum, Mab4H5 and ALMA 6) and to R15 (the alpha 1 and 16-mer antisera) were performed on alternate tissue sections. A VD1/RPD2 neuronal system comprising three classes of neurons (A1-A3) was found. All neurons of the system express the gene. Division into classes is based on immunocytochemical characteristics. Class A1 neurons (VD1 and RPD2) immunoreact with the alpha 1-antiserum, Mab4H5 and ALMA 6. Class A2 neurons (1-5 small and 1-5 medium sized neurons in the visceral and right parietal ganglion, and two clusters of small neurons and 5 medium-sized neurons in the cerebral ganglia) immunoreact with the alpha 1-antiserum and Mab4H5, but not with ALMA 6. Class A3 neurons (3-4 medium-sized neurons and a cluster of 4-5 small neurons located in the pedal ganglion) immunoreact with the alpha 1-antiserum only. All neurons of the system are immunonegative to the R15 antisera. The observations suggest that the neurons of the VD1/RPD2 system produce different sets of neuropeptides. A group of approximately 15 neurons (class B), scattered in the ganglia, immunostained with one or more of the antisera, but did not react with the cDNA probe in in situ hybridization.

L23 ANSWER 12 OF 15 MEDLINE on STN
92146211. PubMed ID: 1723677. Value of anti-human heterogeneous lens culinaris agglutinin reactive AFP monoclonal **antibody** in the diagnosis of primary hepatocellular carcinoma (PHC). Zhang B H. (Institute of Hepatobiliary Surgery, Second Military Medical University, Shanghai.) Zhonghua zhong liu za zhi [Chinese journal of oncology], (1991 Sep) 13 (5) 328-31. Journal code: 7910681. ISSN: 0253-3766. Pub. country: China. Language: Chinese.

AB In this paper, we report on the preparation and application of anti-human heterogeneous AFP-R-LCA monoclonal **antibodies** (VG5, VD12, VB5, VA8, VD1). These McAbs were more sensitive and specific for AFP-R-LCA than the anti-AFP polyclonal **antibody** routinely used. The twin site (a and b) sandwich ELISA method so established was used to test the serum samples of 69 PHC patients, 67 patients with benign liver diseases, 30 pregnant women and 30 normal controls. The results showed that this twin site sandwich ELISA method gave a false positive reaction in only 2.1% and was 81.2% (56/69) positive reaction, giving a positive reaction to 5-100 ng/ml. It was positive in PHC patients with AFP levels less than 400 ng/ml. This method, being simple, accurate and reliable, is valuable in the differential diagnosis of PHC from benign liver diseases.

L23 ANSWER 13 OF 15 MEDLINE on STN DUPLICATE 8
91153865. PubMed ID: 1999354. Rearrangement patterns of T-cell receptor genes in the spleen of athymic (nu/nu) young mice. Palacios R; Samaridis J. (Basel Institute for Immunology, Switzerland.) Immunogenetics, (1991) 33 (2) 90-5. Journal code: 0420404. ISSN: 0093-7711. Pub. country: United States. Language: English.

AB Although the athymic nude mouse is grossly deficient in peripheral T cells, the number of lymphocytes bearing T-cell markers (L3T4, LyT2) and the alpha beta or gamma delta T-cell receptor (Tcr) increases steadily with age. The anatomical site(s) where these cells arise are unknown. Splenocytes from 3-5-week-old C57BL/6 (nu/nu) mice contain 2%-5% Pro-T cell progenitors identified with the Joro 37-5 and Joro 75 **antibodies**, but not mature T cells. To study Tcr gene rearrangement outside the thymus, we fused splenocytes from 3-5-week-old C57BL/6 nude mice with the T-cell lymphoma BW 100.129. Of 22 hybrids that grew stably in culture, four had Tcrd-VD1-D2-J1, two had Tcrd-VD2-J1, and seven had Tcrd-D1-D2 types of rearrangement. Eight hybrids had rearranged the Tcrg-2 gene cluster, but none had rearranged Tcrg-1, -3, or -4. None of the hybrids had rearranged the Tcrb gene cluster and 13 contained DJ rearrangements at the Igh locus. We conclude

that the spleen is one of the extrathymic sites where T-cell progenitors can rearranged Tcrd and Tcrq genes. However, there was no evidence for Tcrb gene rearrangements in this organ. Furthermore, the analysis of this limited number of hybrids suggests that extrathymic Tcr gene rearrangements seem to be distinct and much less diverse than those found in the developing thymocytes.

L23 ANSWER 14 OF 15 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation.
on STN

91:130701 The Genuine Article (R) Number: EZ766. REARRANGEMENT PATTERNS OF T-CELL RECEPTOR GENES IN THE SPLEEN OF ATHYMIC (NU-NU) YOUNG MICE. PALACIOS R (Reprint); SAMARIDIS J. BASEL INST IMMUNOL, GRENZACHERSTR 487, CH-4058 BASEL, SWITZERLAND (Reprint). IMMUNOGENETICS (1991) Vol. 33, No. 2, pp. 90-95. Pub. country: SWITZERLAND. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Although the athymic nude mouse is grossly deficient in peripheral T cells, the number of lymphocytes bearing T-cell markers (L3T4, LyT2) and the alpha-beta or gamma-delta T-cell receptor (Tcr) increases steadily with age. The anatomical site(s) where these cells arise are unknown. Splenocytes from 3-5-week-old C57BL/6 (nu/nu) mice contain 2%-5% Pro-T cell progenitors identified with the Joro 37-5 and Joro 75 **antibodies**, but not mature T cells. To study Tcr gene rearrangement outside the thymus, we fused splenocytes from 3-5-week-old C57BL/6 nude mice with the T-cell lymphoma BW100.129. Of 22 hybrids that grew stably in culture, four had Tcrd-VD1-D2-J1, two had Tcrd-VD2-J1, and seven had Tcrd-D1-D2 types of rearrangement. Eight hybrids had rearranged the Tcrq-2 gene cluster, but none had rearranged Tcrq-1, -3, or -4. None of the hybrids had rearranged the Tcrb gene cluster and 13 contained DJ rearrangements at the Igh locus. We conclude that the spleen is one of the extrathymic sites where T-cell progenitors can rearranged Tcrd and Tcrq genes. However, there was no evidence for Tcrb gene rearrangements in this organ. Furthermore, the analysis of this limited number of hybrids suggests that extrathymic Tcr gene rearrangements seem to be distinct and much less diverse than those found in the developing thymocytes.

L23 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 9
91025668. PubMed ID: 2222891. Neuron-specific monoclonal

antibodies raised against the low molecular weight fraction of a brain homogenate of the pond snail Lymnaea stagnalis immunoreact with neurons in the central nervous system of the cockroach, the guppy, the wall lizard, the rat and man. Kerkhoven R M; Van Minnen J; Boer H H. (Department of Organismic Zoology, Faculty of Biology, Free University, Amsterdam, The Netherlands.) Journal of chemical neuroanatomy, (1990 Sep-Oct) 3 (5) 337-46. Journal code: 8902615. ISSN: 0891-0618. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Monoclonal **antibodies** were raised against the small molecular weight fraction (less than 30 kilodaltons) of an extract from 200 central nervous systems (CNS) of the freshwater snail Lymnaea stagnalis. In a first screening step the supernatants of the 297 emerging hybridomas were immunocytochemically tested on sections of the CNS of L. stagnalis. Sixty-six appeared to produce neuron-specific **antibodies**, five reacted with non-neuronal elements. In a second step the 66 neuron-specific **antibodies** were tested on sections of the CNS of the guppy. Three reacted positively. In the third step the three **antibodies** were tested on the CNS of the rat. One **antibody** (Mab4H5) appeared to give positive results. In the snail brain Mab4H5 stains two identified giant neurons, one in the visceral ganglion (VD1), and one in the right parietal ganglion (RPD2)--these neurons form part of the network controlling the respiratory system--and a small number of cells in the cerebral ganglia (in the anterior and ventral lobes). Ultrastructural observations using immunogold labelling in VD1 showed the antigen to be localized to the secretory vesicles. In the guppy Mab4H5 stains fibres in the tectum and cell bodies in the reticular formation. In rat CNS staining

was observed in Purkinje neurons of the cerebellum, in cortical pyramidal neurons and in neurons and fibres in other brain areas. Subsequent Mab4H5 staining of the CNS of the lizard, the cockroach and parts of the human CNS showed that these tissues also contain Mab4H5-positive neurons. In the human cortex and cerebellum the staining pattern appeared to be similar to that of the rat. On the basis of the results it is hypothesized that the **antibody** reacts with phylogenetically ancient amino acid sequences.

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=> s (debinski w?/au or gibo d?/au)
L24      581 (DEBINSKI W?/AU OR GIBO D?/AU)
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=> s l24 and VEGF-D
L25      12 L24 AND VEGF-D
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=> dup remove l25
PROCESSING COMPLETED FOR L25
L26      5 DUP REMOVE L25 (7 DUPLICATES REMOVED)
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=> d l26 1-5 cbib abs
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L26 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN 2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors. **Debinski, Waldemar** [Reprint Author]; **Gibo, Denise**; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences. Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH). ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L26 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 1
2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors. **Debinski Waldemar; Gibo Denise**; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable brain tumors. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation,

tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of brain tumors. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of brain tumors or for monitoring their progression following initial treatment.

L26 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
 2002:637486 Document No. 137:164115 **VEGF-D** expression in brain cancer in relation to diagnosis and treatment. **Debinski, Waldemar; Gibo, Denise M.** (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB **VEGF-D** serves as a target for diagnosing and treating glioblastoma multiforme and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of **VEGF-D** in the sample. Brain cancer is treated by modulating **VEGF-D** gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with **VEGF-D** binding to a **VEGF-D** receptor.

L26 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
 2003:439275 Document No. 139:83053 **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. [Erratum to document cited in CA136:322910]. **Debinski, Waldemar; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M.** (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551. Publisher: Johns Hopkins University Press.

AB On the cover, "mutliforme" should be "multiforme".

L26 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 2
 2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. **Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M.** (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu). Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein

(GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

=> s l24 and brain cancer
L27 15 L24 AND BRAIN CANCER

=> s l27 and VEGF
L28 1 L27 AND VEGF

=> d l28 cbib abs

L28 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
2002:637486 Document No. 137:164115 **VEGF-D** expression in
brain cancer in relation to diagnosis and treatment.
Debinski, Waldemar; Gibo, Denise M. (The Penn State
Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43
pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF,
CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,
MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.
APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089
20010212.

AB **VEGF-D** serves as a target for diagnosing and treating
glioblastoma multiforme and related **brain cancers**.
Cancer in a brain tissue sample is detected by analyzing expression of
VEGF-D in the sample. **Brain cancer** is treated
by modulating **VEGF-D** gene expression in cells of the cancer, and
by inhibiting angiogenesis associated with the cancer by interfering with
VEGF-D binding to a **VEGF-D** receptor.

=> s l27 and glioblastoma multiforme
L29 1 L27 AND GLIOBLASTOMA MULTIFORME

=> s VEGF-D
L30 791 VEGF-D

=> s l30 and glioblastoma multiforme
L31 7 L30 AND GLIOBLASTOMA MULTIFORME

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L32 3 DUP REMOVE L31 (4 DUPLICATES REMOVED)

=> d 132 1-3 cbib abs

L32 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

2002:637486 Document No. 137:164115 **VEGF-D** expression in brain cancer in relation to diagnosis and treatment. Debinski, Waldemar; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB **VEGF-D** serves as a target for diagnosing and treating **glioblastoma multiforme** and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of **VEGF-D** in the sample. Brain cancer is treated by modulating **VEGF-D** gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with **VEGF-D** binding to a **VEGF-D** receptor.

L32 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

2003:439275 Document No. 139:83053 **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human **glioblastoma multiforme**. [Erratum to document cited in CA136:322910]. Debinski, Waldemar; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551. Publisher: Johns Hopkins University Press.

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L32 ANSWER 3 OF 3 MEDLINE on STN

DUPLICATE 1

2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human **glioblastoma multiforme**. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: **Glioblastoma multiforme** (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together

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=> s VEGF

L33 53874 VEGF

=> s l33 and glioblatoma multiforme

L34 0 L33 AND GLIOBLATOMA MULTIFORME

=> s l33 and brain tumor

L35 482 L33 AND BRAIN TUMOR

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PROCESSING COMPLETED FOR L35

L36 233 DUP REMOVE L35 (249 DUPLICATES REMOVED)

=> s l36 and anti-VEGF

L37 6 L36 AND ANTI-VEGF

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PROCESSING COMPLETED FOR L37

L38 6 DUP REMOVE L37 (0 DUPLICATES REMOVED)

=> d l38 1-6 cbib abs

L38 ANSWER 1 OF 6 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2004:125717 The Genuine Article (R) Number: 767MX. Autocrine pathways of the vascular endothelial growth factor (**VEGF**) in glioblastoma multiforme: clinical relevance of radiation-induced increase of **VEGF** levels. Steiner H H (Reprint); Karcher S; Mueller M M; Nalbantis E; Kunze S; Herold-Mende C. Univ Heidelberg, Dept Neurosurg, Mol Biol Lab, Mol Biol Sect, Neuenheimer Feld 400, D-69120 Heidelberg, Germany (Reprint); Univ Heidelberg, Dept Neurosurg, Mol Biol Lab, Mol Biol Sect, D-69120 Heidelberg, Germany; Univ Heidelberg, Dept Head & Neck Surg, Mol Cell Biol Grp, D-69120 Heidelberg, Germany; German Canc Res Ctr, Div Differentiat & Carcinogenesis, Heidelberg, Germany. JOURNAL OF NEURO-ONCOLOGY (JAN 2004) Vol. 66, No. 1-2, pp. 129-138. Publisher: KLUWER ACADEMIC PUBL. VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS. ISSN: 0167-594X. Pub. country: Germany. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB In tumour-induced angiogenesis of gliomas, vascular endothelial growth factor (**VEGF**) and its receptors fms-like tyrosine kinase (Flt-1) and kinase-insert-domain-containing receptor (KDR) play a major role and are promising targets for tumour therapy. Nevertheless, preliminary results of such therapies could not prove clinical efficacy and thus make a profound knowledge of **VEGF** regulation essential. Based on earlier results, which demonstrated an inhibitory influence of **VEGF** on Flt-1-expressing glioblastoma cells [1], in the present study we focused on the extent of **VEGF** and **VEGF** receptor coexpression and possible therapeutical consequences.

Protein expression of **VEGF**, Flt-1 and KDR was analysed by immunohistochemistry in native tumour tissues of 63 glioblastomas. **VEGF** could be detected in all glioblastomas. Additionally and independently to the expected Flt-1 and KDR expression in tumour

endothelia, we found a coexpression of **VEGF** with Flt-1 in tumour cells of 46 and with KDR in 45 glioblastomas. After exposure of glioblastoma cells to X-ray radiation we observed a strong dose-dependent increase of **VEGF** secretion in two glioblastoma cell cultures by up to 46% and 96%, respectively that originated from an increased **VEGF** mRNA expression. In contrast, under the same conditions secretion of HGF/SF was only slightly elevated and bFGF despite being strongly increased remained at very low overall amounts compared to **VEGF**. Based on previous data on an autocrine function of **VEGF** in Flt-1-expressing glioblastoma cells we hypothesise that the X-ray radiation induced upregulation of **VEGF** might result in a downregulation of tumour cell proliferation and thus lead to a reduced sensitivity to radiation therapy. Therefore our results support the idea that a combination of **anti-VEGF** and radiation therapy might prove a promising new option in fighting against one of the most fatal tumour types.

L38 ANSWER 2 OF 6 MEDLINE on STN

2003245600. PubMed ID: 12712432. Vascular endothelial growth factor-A determines detectability of experimental melanoma brain metastasis in GD-DTPA-enhanced MRI. Leenders William; Kusters Benno; Pikkemaat Jeroen; Wesseling Pieter; Ruiter Dirk; Heerschap Arend; Barentsz Jelle; de Waal Robert M W. (Department of Pathology, University Medical Centre St Radboud, Nijmegen, The Netherlands.. w.leenders@pathol.azn.nl) . International journal of cancer. Journal international du cancer, (2003 Jul 1) 105 (4) 437-43. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB We have previously shown that the dense vascular network in mouse brain allows for growth of human melanoma xenografts (Mel57) by co-option of preexisting vessels. Overexpression of recombinant vascular endothelial growth factor-A (**VEGF**-A) by such xenografts induced functional and morphologic alterations of preexisting vessels. We now describe the effects of **VEGF**-A expression on visualization of these **brain tumors** in mice by magnetic resonance imaging (MRI), using gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA) and ultra small paramagnetic iron oxide particles (USPIO) as contrast agents. Brain lesions derived from (mock-transfected) Mel57 cells were undetectable in MRI after Gd-DTPA injection. However, the majority of such lesions became visible after injection of USPIO, due to the lower vascular density in the lesions as compared to the surrounding parenchyma. In contrast, **VEGF**-A-expressing lesions were visualized using Gd-DTPA-enhanced MRI by a rapid circumferential enhancement, due to leaky peritumoral vasculature. USPIO-enhanced MRI of these tumors corroborated the immunohistochemic finding that peritumorally located, highly irregular and dilated vessels were present, while intratumoral vessel density was low. Our study shows that **VEGF**-A is a key factor in imaging of brain neoplasms. Our data also demonstrate that, at least in brain, blood-pool agent-enhanced MRI may be a valuable diagnostic tool to detect malignancies that are not visible on Gd-DTPA-enhanced MRI. Furthermore, the involvement of **VEGF**-A in MRI visibility suggests that care must be taken with MRI-based evaluation of antiangiogenic therapy, as **anti-VEGF** treatment might revert a tumor to a co-opting phenotype, resulting in loss of contrast enhancement in MRI. Copyright 2003 Wiley-Liss, Inc.

L38 ANSWER 3 OF 6 MEDLINE on STN

2002159150. PubMed ID: 11891967. Dynamic contrast-enhanced magnetic resonance imaging as a surrogate marker of tumor response to anti-angiogenic therapy in a xenograft model of glioblastoma multiforme. Gossmann Axel; Helbich Thomas H; Kuriyama Nagato; Ostrowitzki S; Roberts Timothy P L; Shames David M; van Bruggen N; Wendland Michael F; Israel Mark A; Brasch Robert C. (Contrast Media Laboratory, Department of Radiology, University of California, San Francisco, California 94143-0628, USA.) Journal of magnetic resonance imaging : JMRI, (2002 Mar) 15 (3) 233-40. Journal code: 9105850. ISSN: 1053-1807. Pub. country: United

States. Language: English.

AB PURPOSE: To evaluate the effects of a neutralizing anti-vascular endothelial growth factor (**anti-VEGF**) antibody on tumor microvascular permeability, a proposed indicator of angiogenesis, and tumor growth in a rodent malignant glioma model. MATERIALS AND METHODS: A dynamic contrast-enhanced magnetic resonance imaging (MRI) technique, permitting noninvasive in vivo and in situ assessment of potential therapeutic effects, was used to measure tumor microvascular characteristics and volumes. U-87, a cell line derived from a human glioblastoma multiforme, was implanted orthotopically into brains of athymic homozygous nude rats. RESULTS: Treatment with the monoclonal antibody A4.6.1, specific for **VEGF**, significantly inhibited tumor microvascular permeability ($6.1 \pm 3.6 \text{ mL min}^{-1} 100 \text{ cc}^{-1}$), compared to the control, saline-treated tumors ($28.6 \pm 8.6 \text{ mL min}^{-1} 100 \text{ cc}^{-1}$), and significantly suppressed tumor growth ($P < .05$). CONCLUSION: Findings demonstrate that tumor vascular permeability and tumor growth can be inhibited by neutralization of endogenous **VEGF** and suggest that angiogenesis with the maintenance of endothelial hyperpermeability requires the presence of **VEGF** within the tissue microenvironment. Changes in tumor vessel permeability and tumor volumes as measured by contrast-enhanced MRI provide an assay that could prove useful for clinical monitoring of anti-angiogenic therapies in brain tumors.

L38 ANSWER 4 OF 6 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2001:203420 The Genuine Article (R) Number: 406LC. Correlation of **VEGF** with contrast enhancement on dual-phase dynamic helical CT in liver tumors: Preliminary study. Kwak B K (Reprint); Shim H J; Park U S; Lee T J; Paeng S S; Lee C J; Lim H K; Park C K. Chung Ang Univ, Coll Med, Yongsan Hosp, Dept Radiol, Yongsan Gu, 65 Hangangro 3 Ga, Seoul 140757, South Korea (Reprint); Chung Ang Univ, Coll Med, Dept Radiol, Seoul 140757, South Korea; Chung Ang Univ, Coll Med, Dept Pathol, Seoul 140757, South Korea; Sung Kyun Kwan Univ, Sch Med, Natl Med Ctr, Dept Pathol, Seoul, South Korea; Sung Kyun Kwan Univ, Sch Med, Natl Med Ctr, Dept Diagnost Radiol, Seoul, South Korea; Sung Kyun Kwan Univ, Sch Med, Samsung Med Ctr, Dept Radiol, Seoul, South Korea; Sung Kyun Kwan Univ, Sch Med, Samsung Med Ctr, Dept Pathol, Seoul, South Korea. JOURNAL OF KOREAN MEDICAL SCIENCE (FEB 2001) Vol. 16, No. 1, pp. 83-87. Publisher: KOREAN ACAD MEDICAL SCIENCES. 302 75 DONG DU ICHON, DONG YONGSAN KU, SEOUL 140 031, SOUTH KOREA. ISSN: 1011-8934. Pub. country: South Korea. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The purpose of this preliminary study is to elucidate that vascular endothelial growth factor (**VEGF**) influences contrast enhancement of hepatic tumors on computed tomography (CT). Fourteen patients with hepatic tumors (11 hepatocellular carcinomas; 3 metastatic cancers) underwent a dual-phase dynamic helical CT or computed tomographic hepatic arteriography. The attenuation of each mass was determined as hyperattenuation, isoattenuation or hypoattenuation with respect to the adjacent nontumorous parenchyma. Gun-needle biopsy was done for each tumor, and paraffin sections were immunostained with **anti-VEGF** antibody by the avidin-biotin-peroxidase complex method. The pathologic grade was made by intensity (1+, 2+, 3+) and area (\pm , 1+, 2+). The tumor ranged 2.0-14.0 cm in size (mean, 5.8 cm). In arterial phase, the intensity was not correlated with the degree of enhancement ($p=0.086$). However, the correlation between the attenuation value of hepatic arterial phase and the area of positive tumor cells was statistically significant ($p=0.002$). **VEGF** may be the factor that enhances the hepatic mass with water-soluble iodinated contrast agent in CT.

L38 ANSWER 5 OF 6 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
2000:219618 Document No.: PREV200000219618. Vascular endothelial growth factor, hepatocyte growth factor/scatter factor, basic fibroblast growth

factor, and placenta growth factor in human meningiomas and their relation to angiogenesis and malignancy. Lamszus, Katrin [Reprint author]; Lengler, Ulrike; Schmidt, Nils Ole; Stavrou, Dimitrios; Erguen, Sueleyman; Westphal, Manfred. Department of Neuropathology, University Hospital Eppendorf, Martinistrasse 52, Hamburg, 20246, Germany. Neurosurgery (Baltimore), (April, 2000) Vol. 46, No. 4, pp. 938-948. print. ISSN: 0148-396X. Language: English.

- AB OBJECTIVE: Angiogenesis is mediated by a number of different growth factors and appears vital for tumor growth. The understanding of angiogenic mechanisms could offer new therapeutic perspectives; in this context, the role of four potentially angiogenic growth factors was analyzed in a large series of meningiomas of different grades. METHODS: Vascular endothelial growth factor (VEGF), placenta growth factor, hepatocyte growth factor/scatter factor, and basic fibroblast growth factor were quantified in 69 tumors by enzyme-linked immunosorbent assay. Microvessel density and proliferative activity were determined on paraffin sections, and clinical tumor invasiveness was rated. Induction of endothelial chemotaxis and capillary-like tube formation were studied in vitro using modified Boyden chamber assays and three-dimensional collagen gel assays, respectively. RESULTS: Tumors included 40 benign (World Health Organization (WHO) Grade I), 21 atypical (WHO Grade II), and 8 anaplastic/malignant (WHO Grade III) meningiomas. We found a correlation between meningioma grade and VEGF content ($r = 0.37$, $P = 0.002$), which was 2-fold higher in atypical than in benign meningiomas ($P = 0.022$) and 10-fold higher in malignant than in benign meningiomas ($P = 0.025$). Among different subtypes of Grade I meningiomas, VEGF levels were 10-fold higher in meningothelial than in fibrous meningiomas ($P = 0.015$). None of the other three factors investigated showed any association with tumor grade, microvessel density, or invasiveness, and VEGF also did not correlate with vascularity or invasiveness. Moreover, vascularity did not increase with malignancy grade. Endothelial chemotaxis and capillary-like tube formation in vitro were induced by meningioma extracts and were most effectively blocked by co-addition of antibodies against basic fibroblast growth factor, followed by anti-VEGF, whereas anti-hepatocyte growth factor/scatter factor was not effective. The chemotactic activity of meningioma extracts on endothelial cells correlated with their VEGF content ($r = 0.6$, $P = 0.003$). CONCLUSION: Meningiomas do not show an angiogenic switch involving VEGF and/or hepatocyte growth factor/scatter factor, as has previously been found in gliomas. Nevertheless, the biological activity of VEGF and basic fibroblast growth factor in meningiomas suggests that both are potential targets for antiangiogenic therapy in meningiomas of all WHO grades.

L38 ANSWER 6 OF 6 MEDLINE on STN

1999232994. PubMed ID: 10218626. Mechanisms of angiogenesis in the brain. Plate K H. (Department of Neuropathology, Neurocenter, Freiburg University Medical School, Germany.) Journal of neuropathology and experimental neurology, (1999 Apr) 58 (4) 313-20. Ref: 62. Journal code: 2985192R. ISSN: 0022-3069. Pub. country: United States. Language: English.

- AB Brain angiogenesis is a tightly controlled process that is regulated by neuroectodermal derived growth factors that bind to tyrosine kinase receptors expressed on endothelial cells. In the rat brain, angiogenesis is complete around postnatal day 20, but endothelial cells can proliferate in the adult brain under pathological conditions such as hypoxia/ischemia and brain tumor growth. Current evidence suggests that physiological angiogenesis in the brain is regulated by similar mechanisms as pathological angiogenesis induced by tumors or by hypoxia/ischemia. The hypoxia-inducible endothelial cell mitogen and vascular permeability factor, vascular endothelial growth factor (VEGF) appears to play a pivotal role in most of these processes. VEGF is expressed when angiogenesis is high, as in embryonic neuroectoderm, in glioblastomas and around infarcts, but is expressed at low levels when angiogenesis is absent, as in adult neuroectoderm. Since growth factors such as VEGF and angiopoietins and their

receptors appear to be necessary for angiogenesis, targeting of growth factor/receptor pathways for angiogenesis-dependent diseases such as glioblastoma might be useful for therapy. Several compounds, including **anti-VEGF** antibodies and VEGFR-2 inhibitors are currently in clinical trial. On the other hand, induction of angiogenesis by growth factors (pro-angiogenesis) might prove to be a rational therapy for patients with stroke.

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VEGF-D is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme.

Debinski W, Slagle-Webb B, Achen MG, Stacker SA, Tulchinsky E, Gillespie GY, Gibo DM.

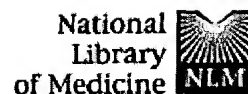
Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA. wdebinski@psu.edu

BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (VEGF-D), is the newest mammalian member of VEGF family. We analyzed VEGF-D in GBM because of its high angiogenic potential and its linkage to the X chromosome.

MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of VEGF-D, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays.

RESULTS AND CONCLUSIONS: GBM expressed ubiquitously VEGF-D, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced VEGF-D expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and VEGF-D levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because VEGF-D activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The VEGF-D system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

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Characterization of an established human, malignant, glioblastoma cell line (GBM) and its response to conventional drugs.

Perego P, Boiardi A, Carenini N, De Cesare M, Dolfini E, Roberto-Giardini, Magnani I, Martignone S, Silvani A, Soranzo C, et al.

Division of Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

A cell line, GBM, was established from a human malignant glioblastoma and was characterized with particular reference to its response to conventional drugs. The GBM cell line exhibited a 73 ± 7 h doubling time in monolayer cultures. Expression of glial fibrillary acidic and S-100 proteins was observed. Karyotype analysis of GBM cells at early passages revealed the presence of two near-triploid clones (A and B) with multiple chromosome rearrangements; a 100% frequency for clone B was observed in the established cell line. GBM cells had tumorigenic properties, since the s.c. injection of cultured cells into nude mice gave rise to slowly growing tumors. The morphology of GBM cells was retained during in vitro and in vivo passages, as judged by light microscopy. GBM cells were relatively resistant to most conventional drugs; among the tested drugs, only taxol exhibited a marked cytotoxic effect comparable to that found in cells of a different tumor type. GBM cells were found positive for the epidermal growth factor receptor, HER2-neu and P-glycoprotein by flow cytometry of cells labelled with monoclonal antibodies. In spite of the expression of relatively high gamma-glutamyltransferase activity, the intracellular glutathione level was comparable to that of other chemosensitive tumor cells. This glioblastoma cell line is a suitable model for the identification and preclinical studies of new agents and provides an additional system to explore the molecular basis of the intrinsic drug resistance of glioblastoma.

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Models for assessment of angiogenesis in gliomas.

Goldbrunner RH, Wagner S, Roosen K, Tonn JC.

Department of Neurosurgery, University of Wuerzburg, Germany.

In the last two decades, much attention has been focussed on mechanisms of glioma vascularization including the investigation of growth factors and receptors involved. Recently, these efforts resulted in various approaches for antiangiogenic treatment of experimental brain tumors. These basic science and preclinical trials need an assortment of models, which should allow investigating a variety of questions. Several objectives concerning basic endothelial cell (EC) characteristics can adequately be studied in vitro using EC monolayer assays. Three-dimensional spheroid techniques respect the more complex cell-cell and cell-environment interplay within a three-dimensional culture. To optimize the imitation of the crucial interaction of human gliomas with host endothelial cells, immunological cells and extracellular matrix, animal models are mandatory. An essential rule is to utilize an orthotopic model, since tumor-host interaction is organ specific. To avoid alloimmunogenic responses, it is desirable to use weakly or not immunogenic glioma grafts, what is best accomplished in a syngeneic model. However, since rat gliomas poorly resemble human glioma growth patterns, human glioma xenografting into immunocompromized animals should be considered. In vivo monitoring techniques like videoscscopy via a cranial window or magnetic resonance imaging (MRI) allow for functional studies and improve the validity of the model employed. Finally, it is essentially to recognize the limitations of each model considered and to select that model, which seems to be most appropriate for the objectives to be investigated.

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